COVER PAGE

EFFICACY TEST PROTOCOL SPC-001

EFFICACY TEST OF PICARIDIN-BASED PERSONAL INSECT REPELLENTS WITH MOSQUITOES UNDER FIELD CONDITIONS

SYNOPSIS

Picaridin is a synthetic arthropod repellent developed as an alternative to DEET. Spectrum Division of United Industries Corp. proposes to replace all product performance studies for its Picardin-based repellents to bring them up to date with current Agency policy. In his letter dated 18 April 2007, Mr. Richard Gebken of the Agency's Registration Division spelled out the requirements to meet that goal. For a total of eight currently registered Spectrum products, efficacy testing will be conducted with three. Efficacy data from our tests of 7% Picardin Pump Spray will serve for that product and will also be adopted for 10% Pump Spray and Aerosol formulations, as well as for a 5.75% Towelette. Data from 15% Pump Spray will be used for that product as well as for 15% Aerosol and 12% Towelette. (Both Towelette formulations are simply the corresponding Pump Spray formula placed onto an inert fabric substrate.) The third test article is a 15% Picaridin Lotion formulated with sunscreen. It will be tested independently because interactions between repellency and sunscreen may make it substantively different from the other 15% formulations.

This protocol, dated 13 July 2007, was reviewed and approved by a private IRB, the Independent Investigational Review Board (IIRB), located in Plantation Florida, on 17 July 2007. The document in hand is that which IIRB reviewed, with the addition, on 17 July 2007, of the following elements for review by the United States Environmental Protection Agency, including its Human Studies Review Board: 1) This completed cover page; 2) the approved, signed Informed Consent Form, which replaces the proposed Informed Consent Form we submitted to IIRB; 3) record of PI–IIRB correspondence. The Table of Contents on the next page reflects those changes and additions.

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TABLE OF CONTENTS

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1 TITLE: EFFICACY TEST OF PICARIDIN-BASED PERSONAL INSECT REPELLENTS WITH MOSQUITOES UNDER FIELD CONDITIONS

2 PROTOCOL NUMBER:

SPC-001

3 SPONSOR:

Spectrum Division of United Industries Corporation (hereinafter referred to as 'Spectrum' or 'Sponsor')

3.1 Address:

Spectrum Brands, Inc.
13260 Corporate Exchange Dr.
Bridgeton, MO 63044

4 PROTOCOL OBJECTIVE:

4.1 Type of Protocol:

This protocol will indicate the specific methods to be used, and direct the conduct of, Study SPC-001. The study will be conducted in the laboratory at the letterhead address and at locations in nature with mosquitoes.

5 STUDY OBJECTIVE, RATIONALE AND STANDARDS:

5.1 Objective of Research:

The objective of this study is to test the repellent efficacy characteristics of the test materials to mosquitoes. The active ingredient, Picaridin, is of known high broad-spectrum efficacy, but has not been studied at very many formulations in the U.S. The general hypothesis of the research is that the test materials will substantially reduce the probability that a mosquito bites a subject for several hours. However, more than testing that hypothesis, the aim of the research is to characterize the duration of repellency based on the Complete Protection Time criterion.

Complete Protection Time, or CPT, is defined herein as the time between application of test material and the First Confirmed 'Landing with Intent to Bite.' A 'Landing with Intent to Bite', or 'LIBe', occurs when a mosquito alights on a subject's treated test skin and extends its proboscis to the skin surface while ceasing locomotion. A 'First Confirmed LIBe' is that which is followed by another within 30 minutes. The work conducted pursuant to this protocol will be initiated by determining the amount of each of the repellents that subjects typically apply. Dosimetry will consist of a behavioral assay.

5.2 Rationale and Main Endpoint:

As part of its review of Spectrum's Picaridin formulations, the U.S. EPA has specified additional efficacy data to be collected as a condition of registration. The rationale for this study is to provide those efficacy data. The information will also be used as the basis for accurate product labeling.

This study will test the efficacy of three formulations. Picaridin-based repellents have been marketed around the world for a decade, but the product is comparatively recent in the U.S. market, where Spectrum introduced it in 2005. The U.S. Centers for Disease Control has acknowledged the existence of substantial consumer interest in new and effective insect repellent products, and that Picaridin-based repellents are among the very few of sufficiently high efficacy to offer reliable personal protection against vectors of West Nile virus (in

April 2005). However, few Picaridin products are currently marketed in the U.S. Thus, there is substantial merit in the development and unconditional registration of new Picaridin-based repellent products.

Information regarding the stability of the end products is available from the Sponsor in a separate study.

The main endpoint of this study will be the conclusion of a mosquito repellent efficacy field test of Picaridin-based topical repellents, with the data set suitable for submission to U.S. EPA to comply with the conditions of registration, and including the bridging of performance data to related products. The efficacy study will consist of two field trials. In each trial, the Picaridin formulations will be tested with 10 subjects, with two untreated control subjects. Initial dosage determination ('dosimetry') will also be conducted with 10 subjects per formulation, some of whom may then go on to participate in efficacy testing. Dosimetry will be conducted at the letterhead address. When 10 subjects have completed dosimetry for each formulation, the resulting data will be used to determine dosing for the efficacy testing.

5.3 Rationale for use of Human Subjects:

Human subjects are required because they represent the target system for the test material; sufficiently reliable replacement models for repellency testing do not exist. In addition, subjects will self-administer the test articles during dose determination. 10 subjects are required in order to reduce variation around the population means which we will describe.

5.4 Balance of Risks and Benefits:

The study-associated risks are of three types: exposure to test materials, exposure to biting arthropods and possible exposure to vectors of arthropod-borne diseases. As described below, subject health and safety are unlikely to be impacted by any study-associated risks during or after the study.

The repellent's active ingredient has a low acute and chronic risk profile, a fact established through experimentation and through a history of consumer use. The concentrations of the active

ingredient in the products being tested are similar to those of other products which EPA has recently registered. Subjects with known allergic reactions to insect repellents and common cosmetics are excluded from participating.

'Repeat' exposures during dosimetry are of brief duration before the product is washed off, and the likely total exposure time is much shorter than a typical single consumer application. Risks associated with inhalation and ingestion would only ensue from serious mishandling by subjects, a scenario that the study methods preclude.

The risk of skin reactions to a mosquito bite is reduced by excluding candidate subjects who are aware of having a history of such reaction. In addition, subjects will be trained to quickly remove any mosquitoes that attempt to bite them, before penetration or injection of saliva if possible. Moreover, a stopping rule instructs subjects to cover any treated skin immediately if more than one mosquito attempts to bite during any exposure period. Subjects will be exposing small areas of treated skin for only 4 minutes per hour. Other parts of the body will be protected with provided gloves, head nets and full bodysuits made of Tyvek, through which mosquitoes do not bite. Subjects will be teamed with a partner for joint observation. Experienced technical personnel will be present at all times for assistance.

The U.S. Centers for Disease Control estimates that about 1 in 5 people who become infected with West Nile virus develop West Nile fever. Subjects are instructed to be alert for any flu-like symptoms (unusual tiredness, unusually severe headaches, body aches, fever), glandular swelling or a rash on the trunk of the body, for up to two weeks after the test. About 1 in 150 infected people develop more serious symptoms, which will be described to the subjects. Most people (about 4 in 5) who are infected with West Nile virus do not develop any type of illness.

In addition, the techniques employed to minimize exposure to mosquitoes and mosquito bites render the possibility of contracting a mosquito-borne disease very low. Field tests will be conducted in an area where such viruses have not been detected by county and state health or vector/mosquito control agencies for at least a

month, so the risk is probably low that any individual mosquito present carries a disease. In each trial, only two experienced, qualified subjects (qualification criteria described in §9.1) will expose untreated limbs to monitor biting pressure, at the same infrequent, brief intervals as treated subjects, and with multiple assistants to remove any mosquitoes that land with intent to bite.

In summary, the combination of technical precautions and natural factors means that the chances that any subject will contract West Nile fever or another disease from a mosquito bite are extremely small. There is probably no more risk to subjects than they would experience when engaged in normal outdoor activities in a similar rural area at the same time of year. If at any time during the study, a subject suffers a skin reaction or feels ill, he or she is instructed to inform the Study Director (i.e., the 'Principal Investigator'), or any other technical personnel who are present to direct the study. Such subjects will be immediately withdrawn from testing; medical management will then be implemented (see §9.5, below). Subjects may also request access to standard first-aid materials (such as bandages, antiseptics and mild topical and oral antihistamines) and request qualified first-aid assistance at any time. EpiPen® will also be available in case of a Type 1 (anaphylactic) allergic reaction. At least one qualified researcher will remain with the other test subjects if other researchers depart with an injured or ill subject. Subjects are clearly and repeatedly informed that they may remove themselves from the study for any reason at any time, without penalty to their compensation.

Balanced against these slight risks are substantial and reasonably likely benefits. The principal beneficiary will likely be the Sponsor, for whom new data and new labeling will meet current U.S. EPA registration standards. Spectrum is a major marketer of insect repellents in the U.S., primarily under the Cutter® label. Insect-borne disease is of growing significance in the U.S. and around the world where U.S. citizens are active. Moreover, discomfort associated with nuisance biting restricts many work and pleasure activities. A test such as the one proposed here is the Sponsor's only legitimate path toward further product development and greater availability of new Picaridin-based mosquito repellents to U.S. consumers.

5.5 Standards Applied:

U.S. EPA Good Laboratory Practice Regulations (40 CFR 160); 40 CFR 26 subparts K and L; FIFRA §12(a)(2)(P); California State EPA Department of Pesticide Regulation study monitoring (California Code of Regulations Title 3, §6710).

6 INVESTIGATIONAL AND TEST MATERIAL CONTROL:

6.1 Test Substance:

6.1.1 Description of the Test Materials:

7% Picardin Pump Spray (data will be bridged to 10% Pump Spray and Aerosol and 5.75% Towelette).

15% Picaridin Pump Spray (data will be bridged to 15% Aerosol and 12% Towelette).

15% Picaridin Lotion formulated with sunscreen.

Note that the Towelette formulations are simply the corresponding Pump Spray formulae placed onto an inert fabric substrate.

6.1.2 Dosage Form:

Lotion and Pump Spray applied to the skin.

6.1.3 Trade Name:

Cutter.

6.1.4 Dose:

Determining dosage is part of this study's main objective. Dosage for repellency testing will be the mean of the subject means determined for each product in the dosimetry portion of this study. Dosage will be measured in weight and reported by weight and volume. Dosimetry data will be

shared with the related repellent efficacy study detailed in the companion protocol SPC-002.

6.1.5 Manufacturing Site:

TBD

6.1.6 Test Material Storage During Study:

Prior to application, the test materials will be stored indoors, at room temperature and away from direct sunlight or direct sources of moisture, and according to any conditions specified by the Sponsor. Storage will be at Carroll-Loye Biological Research in Davis, CA.

6.1.7 Test Material Safety:

EPA regulates use of inert ingredients (also termed "other" ingredients) by toxicology profiles in animal tests and by their inclusion in EPA lists of "approved" other ingredients. The insect-repellent products proposed for testing have been tested on animals for potential oral and dermal toxicity. The active ingredient (Picaridin) has an extensive toxicity data file, has been previously registered by EPA and has a positive safety record in consumer use. MSDS files for the products we propose to test are appended.

6.1.8 Test Material Composition and Stability:

The test material formulations are typical of topical cosmetics and insect-repellent products marketed to consumers. They will be produced under applicable Good Laboratory Practice standards, with records available to EPA. They will be couriered to Carroll-Loye Biological Research, with Chain-of-Custody documented. After that, they will be stored at the Carroll-Loye offices in a closed cabinet at room temperature (approximately 19-27°C). The composition and content of the products' active ingredient used for the proposed efficacy studies will be confirmed by analytical methods prior to and following human subject efficacy testing. The Sponsor believes that the formulations

will be stable for the duration of the study, based on previously conducted storage-stability studies. The EPA has extensive experience with enforcing requirements for such tests based upon their history with similar products applied to humans. Spectrum intends to provide any requested information as appropriate to safety and efficacy issues.

6.2. Negative Control:

6.2.1 Description of the Negative Control:

The negative control is untreated for both dosimetry and repellency assays.

6.2.2 Rationale for Employing a Negative Control:

Dosimetry testing requires an untreated control for the assumption that dosimeters will not gain appreciable weight from contract with untreated skin.

Repellent efficacy can only be measured in the presence of biting mosquitoes. In addition, the duration of repellency recorded is likely a function of the number of host-seeking mosquitoes active during the study. The U.S. EPA uses a standard minimum rate of mosquito attack on untreated subjects to ensure that the repellents under study are sufficiently challenged to provide meaningful data. Traditionally, the measure rate is termed the 'ambient biting pressure.' We adopt that value, but use LIBes ('Landings with Intent to Bite') rather than bites. A mean study LIBe rate of approximately 1 LIBe per untreated (negative control) lower leg or lower arm per 1 minute is required.

We take several precautions to minimize the probability that untreated control subjects receive any bites (see §§5.4, 8.2, 8.3.1, 8.4.1, 10.4.6). Recognizing that individual subjects differ in their inherent attractiveness to mosquitoes, U.S. EPA science reviewers recommended that we use two untreated control subjects for this study in order to improve the likelihood of sampling ambient biting pressure in a

representative fashion, while still exposing a very small number of untreated subjects to risks from foraging mosquitoes. Having separate untreated subjects also circumvents the problem of interaction between treated and untreated limbs that may arise when subjects serve as their own simultaneous controls. In reviewing a similar protocol in May 2006, the California Department of Pesticide Regulation initially requested use of a single negative control, but compromised at two such subjects based on U.S. EPA's position. The prospect of receiving approval to use more than two untreated control subjects is probably small in this case.

There are no controls by which the formulation matrices without the repellent active ingredient are tested. There is no a priori basis for anticipating significant repellent activity in the matrices, and the study objective is to examine efficacy of the end products. The question of whether there is interaction between matrix and active is external to that objective. Accordingly, the added risk of including additional subjects testing matrix-only formulations cannot be justified.

6.3 Comparison Article:

None.

6.4 Test Arthropod Species:

Testing will be conducted with all or some of wild *Aedes vexans*, *Aedes melanimon, Aedes taeniorhynchus, Culex tarsalis* and *Culex pipiens* mosquitoes, and possibly other mosquito species that occur in the same habitats. Mosquito specimens will be collected from untreated control subjects and from the protective clothing of all subjects during testing and identified in the laboratory using taxonomic keys and stereomicroscopy.

7 STUDY SCHEDULE:

7.1 Proposed Date of Initiation:

To be determine (TBD); within one year of IRB approval.

7.2 Schedule of Events:

Test day	Date	Activities
-30 to -2	TBD	Begin subject recruitment. Introduce subjects to test plan and procedures; explain compensation; review subject rights and consent forms; provide option to sign consent forms to participate. Measure limb surface areas; determine individual dosing behavior and rates, mean dosing rates and individual dosage values.
1-2	TBD	Prepare individual dosages for application. Meet with subjects to review day plan and safety procedures. Administer repellent, or do so after travel to field site. Travel to field site. Review safety and data-collection procedures. Commence repellency data collection. Monitor subject safety, comfort, comportment and compliance with data-collection protocol.

7.3 Proposed Date of Completion:

Experimental Completion Date (Test Day 1): TBD.
Final Report Completion Date: TBD.

8 STUDY DESIGN:

8.1 Treatment Groups:

For efficacy testing of each test material, there are two experimental groups: 1) a ‘treated’ group of subjects treated with a single test product, and 2) an ‘untreated’ (‘negative’) control group. The dosimetry study is an examination of dosing behavior for each test material. In that study, each subject will be treated,

and will also serve as his or her own untreated control for the dosimeters.

8.2 Experimental Design:

The experiment will be partially randomized by subject. Because the treated condition will be evident to experimenters and subjects, and the test materials are readily distinguishable (opaque lotion versus clear, low-viscosity liquid), neither group will be effectively blinded. The obvious, relatively conservative criteria on which failure is determined (confirmed landing with intent to bite) will help to eliminate any influence of experimenter or subject bias. Also note that for subject safety, control subjects will be chosen only from among individuals that are experienced in entomological testing or biological science (see §8.3.1, below). Whether arms, legs or both are tested at a given site will depend on the species of mosquitoes present and their behavior. That decision will be made based on reconnaissance of the field sites prior to data collection.

8.3 Randomization Procedures for Repellent Efficacy Testing:

8.3.1 Allocation of subjects to treatment groups:

All subjects that are not untreated controls will be assigned to the treatment group. Treatments will be balanced between arms and legs if both limbs are used. Negative control subjects will be selected exclusively from among experienced personnel. To be regarded as experienced personnel, a candidate subject must have an undergraduate (or more advanced) degree in the life sciences, or be a vector-control professional, or have participated in at least five prior Carroll-Loye repellent efficacy studies. In addition, that person must meet all of the other participation criteria listed in §§9.1.1.1 and 9.1.1.2.

8.3.2 Treatment allocation table:

Materials will be distributed among subjects as tabulated below. Also included are 2 additional personnel (Subjects 31 and 32) who will monitor ambient biting pressure with untreated limbs during the test.

Subject	Lotion	7% Pump	15% Pump	Untreated
1	X			
2	X			
3	X			
4	X			
5	X			
6	X			
7	X			
8	X			
9	X			
10	X			
11		X		
12		X		
13		X		
14		X		
15		X		
16		X		
17		X		
18		X		
19		X		
20		X		
21			X	
22			X	
23			X	
24			X	
25			X	
26			X	
27			X	
28			X	
29			X	
30			X	
31				X
32				X

8.4. Conditional Boundaries or Limits of Study:

8.4.1. Ambient ‘Landing with Intent to Bite’ Pressure:

A mean study LIBe ('Landing with Intent to Bite') rate of ≥ 1 LIBe per untreated (negative control) lower leg or lower arm per 1 minute is required. No more than 10% '0' values for individual exposure periods are permitted. Ambient LIBe pressure is measured from continuous exposure during 1-minute exposure periods commencing once every 15 minutes, beginning at the onset of data collection. Negative control subjects are attended by 2 assistants using mechanical aspirators to remove all mosquitoes that LIBe before biting commences.

8.5. Monitoring of Environmental Conditions During the Study:

Records will be made of environmental conditions (temperature, relative humidity, wind speed, light intensity and precipitation (presence/absence and general rate/quality) at approximately 1-hour intervals throughout the field trial.

9 STUDY PROCEDURES:

9.1 Test Subjects:

9.1.1 Inclusion criteria, all subjects:

9.1.1.1	Age:	18-55 years
9.1.1.2	Sex:	Male/female
9.1.1.3	Race:	Any race
9.1.1.4	Written consent: (see 9.4, below)	
9.1.1.5	Language:	Speak and read English

9.1.2. Inclusion criteria specific to the 2 untreated subjects:

9.1.2.1 To qualify for candidacy as a subject who exposes untreated skin, an individual must be regarded as competent to do so by the Principal Investigator, must have participated in at least five prior Carroll-Loye repellent efficacy trials, or have participated in at least three such trials and have at least two years of experience as a

college life sciences major, or be professionally employed in vector-control services.

9.1.3 Exclusion criteria, all subjects:

9.1.3.1	Known to be hypersensitive to mosquito bites or exhibiting hypersensitivity during test.
9.1.3.2	Known to be sensitive or showing sensitivity to any of the test product ingredients after application.
9.1.3.3	Poor physical condition.
9.1.3.4	Unwilling to submit to brief query about personal condition.
9.1.3.5	Use of insect repellent within 1 day preceding the study.
9.1.3.6	Unwilling to refrain from use of perfumed products, alcoholic beverages or smoking after 9 p.m. the evening preceding the test and throughout the test.
9.1.3.7	Known to be pregnant or lactating. Pregnancy will be self-checked by each female volunteer on the morning of the repellent test using an OTC test kit provided by Carroll-Loye. Results of each such test will be immediately verified by direct inspection by a female technician trained to make that assessment. Only volunteers scored as nonpregnant will be allowed to participate.
9.1.3.8	Unable to deliver the test materials to own left and right limbs.
9.1.3.9	Unable to see mosquitoes on skin or otherwise effectively monitor and remove mosquitoes that alight on skin.
9.1.3.10	Student or employee of the Study Director.
9.1.3.11	Does not regularly spend time in outdoor settings.
9.1.3.12	Withdraws from testing before receiving a confirming LIBe, when the total exposure duration is less than 90% of the mean of subjects who did not withdraw, and when not more than 2 of 10 subjects have so withdrawn.

If more that 2 of 10 subjects withdraw prematurely, those with the briefest participation will be replaced first. This exclusion factor is not automatically invoked if the Study Director ends exposures due to other factors, such as darkness; in such cases, the data collected before termination may be sufficient to meet the study goals.

9.1.4 Number of Subjects and Rationale for Sample Sizes:

In efficacy testing, we will use 10 subjects per treatment and 2 untreated control subjects per field trial. In the dosimetry portion of the study, 10 subjects will be engaged to apply each repellent. Each subject is a replicate.

The number of subjects is chosen as a compromise between several conflicting factors. In the absence of clear means of estimating the distribution of outcome values, it is difficult to predict an ideal sample size. From a strictly scientific standpoint, an appropriate response under such circumstances would be to increase the sample size, but ethical and economic considerations demand the opposite in the present study, particularly during the efficacy testing phase.

The U.S. EPA has historically required a minimum of 6 subjects for repellent efficacy testing. Given that test repellents are nearly certain to exhibit greater than zero efficacy, and that testing is conducted under adequate ambient biting pressure, it is nearly certain that no untreated subjects will register fewer or later LIBes than any treated subjects. As a result, from the standpoint of statistical power, 6 treated subjects and 1 untreated subject are sufficient to demonstrate a significant treatment effect at $P<0.05$ (one-tailed test in which all treated values differ in the same direction from the untreated). Along the same vein, 6 is often regarded as a statistically sufficient sample for an observation subset because the increment in the confidence of means estimate begins to drop off sharply at that point. Notably, under the historical guidelines, there seem to have

been few problems with EPA registering repellents that commonly fail to meet their labeled performance specification.

The main scientific risk of using a very small sample is that the probability of over-representing subjects inherently unattractive to mosquitoes is rather large. Note, however, that for U.S. EPA registration purposes, the test for mosquito repellency is conducted twice, once in each of 2 ecologically different habitats. In our experience, some or all of the subjects in one test normally do not participate in the other. In addition, 2 negative controls are used for a more robust baseline comparison. Those facts substantially decrease the probability of such sampling error.

However, further considerations indicate that a somewhat larger sample would be superior. Note that the draft EPA guidelines state that the response variable, 'Time to First Confirmed Bite' (or LIBe in this study) is calculated as the average duration for all treated subjects. There is no consideration of variation. In any given study, increasing the number of treated subjects to 10 will improve the probability of accurately estimating the population mean.

The 95% confidence interval computation is useful for assessing the certainty of a means estimate, and for a normal probability density function, that interval is ±1.96 standard error of the mean. In this study, we anticipate that the distribution of Times to First Confirmed LIBe will be truncated toward the origin. Because available mean and variance data on efficacy (e.g., Carroll[1]) indicate that no individual values will be near zero, approximating the exponential model with the normal model is likely justifiable. Using the rule of thumb that a distribution in which the mean is greater than 3 standard deviations above zero may be regarded as effectively normal, it is sensible to compute and report the normal 95% confidence interval in this study. Alternatively, if tests indicate substantial

[1] Carroll, S. P. (2006) Evaluation of topical insect repellents and factors that affect their performance. Chapter 12 in *Insect Repellents: Principles, Methods, and Use,* Debboun, M., Strickman, D. and Frances, S. P. (eds.). Boca Raton, Florida, CRC Press.

deviation from a normal distribution, the deviation will be corrected prior to analysis. An exception would be cases in which there is frequent truncation of records ('data censoring') due to subject withdrawals before product failure. In that case, other means of analysis (Kaplan-Meier survival analysis, §11.3.1) will be employed, but that possibility is not strongly related to sample size considerations.

To consider an example, in a study of repellency employing 8 subjects, Cilek et al.[2] recorded a mean protection time of approximately 180 minutes, with a standard error of about 15 minutes. Had the *N* been 6, we can roughly predict that the 95% CI would be 148-212. At *N*=10, the estimate would be 155-205. At *N*=20, the interval would be roughly 162-198. Evidently, adding the additional 10 subjects to reach an *N* of 20 shrinks the interval, in absolute terms, no more than did the addition of 4 subjects to increase the sample size from 6 to 10.

To summarize, in the case of a highly efficacious repellent, adding subjects beyond 6 is likely to increase the precision of the means estimate only slowly. However, the regulatory justification for this study is predicated on an aversion to assuming that efficacy is closely predictable in new formulations. That conservatism is further justified on the basis of the individual and public health importance of avoiding inaccuracy in this study. That position, coupled with the fact that data collection is only 'replicated' once (in a different habitat at that), argues for a prudent approach. To reduce the risk of over-representing atypically attractive subjects, as well the weight of the value obtained from any one subject, we regard 10 (rather than 6) treated subjects as a better sample size for the repellency portion of the study.

9.1.5 Individual subject influences on repellent performance and risks from participation, in relation to the choice of subjects:

[2] Cilek, J. E., Peterson J. L. and Hallmon, C. F. (2004). Comparative efficacy of IR3535 and DEET as repellents against adult *Aedes aegypti* and *Culex quinquefasciatus*. J. Amer. Mosq. Control Assoc. 20: 299-304

Carroll[1] reviewed the factors that influence the performance of insect repellents and concluded that there is no *a priori* means of predicting an individual's attractiveness to a particular mosquito population, or likely impact on a repellency trial's data set. Several studies have indicated that individuals differ in attractiveness to mosquitoes, but individual attractiveness rankings shift substantially among mosquito taxa. Skin-emanated volatiles influence attractiveness, as do skin temperature and absorption properties; these factors may likewise influence repellent efficacy.

The search for general characteristics that predict repellent performance has led to studies of gender, age, race, hair color, complexion, weight, skin moisture, menses (females), hairiness and sweat. Of these, only gender has been shown to have strong and significant individual effects, in 2 studies with adequate sample sizes. One of these studies found females to be 25% less attractive to *Aedes* mosquitoes (than are males), while the other study showed that females using DEET are significantly less protected against *Anopheles* mosquitoes (than are males using DEET) – the opposite pattern. That difference is consistent with further findings that the type of repellent used also interacts complexly with individual subjects and mosquito species in determining efficacy. Nonetheless, because gender effects seem most plausible, we will attempt to engage similar numbers of males and females.

For clarity, note, for example, that studies have shown that sweating increases attractiveness to at least 1 mosquito species. What is not clear is whether individuals that tend to sweat more than others are generally more attractive to mosquitoes.

On the other hand, it *is* clear that conditions of use strongly influence repellent performance. We intentionally limit our testing to places and times where large number of mosquitoes are active. Further, we expose subject individuals as uniformly as possible to those mosquitoes, and have them engage in behaviors resembling common

outdoor activities (walking, sitting, reaching) that may be attractive to mosquitoes. Subjects are monitored to prevent exposure of treated areas to external moisture or abrasion.

Analogous to the summation for repellency, there are few clear patterns permitting us to predict which individuals might be at relatively greater risk from participating in this study. Pregnant and lactating women are excluded on general medical principals, and persons over age 55 are excluded due to slightly elevated health risks from West Nile fever (see above), though the likelihood of contracting the causal agent during a repellent test is very low.

9.1.6 Choice of subjects and recruitment:

9.1.6.1 Sampling Frame of Study Subjects:

For reasons of practicality and control, we work with people from the community in which our business is located: Davis, CA. Davis is a university-dominated community, so the population demography differs somewhat from non-university communities. Based on census data, the 4 major race/ethnicity groupings in the local population are: 70% Caucasian, 15% Asian, 8% Hispanic and 2% African-American (these are approximate numbers).

Initial contact is through word of mouth and telephone contact with subjects who have participated in similar previous Carroll-Loye repellent efficacy tests and have agreed or requested to be in our Volunteer Database. At present, that database consists of 30 males and 28 females. Of the 58 total subjects, 44 (76%) identify themselves as Caucasian, 8 (14%) as Asian, 3.5 (6%) as Hispanic and 2.5 (4%) as African-American. These proportions match the city's racial distribution quite closely.

75% of the subjects are range in age from 20 to 40; the remainder are between 40 and 55. Educational levels are as follows: 7 with a Ph.D., 8 with an M.S., 18 currently in graduate programs, 14 with a B.S. or B.A., and 10 undergraduate students. Among those who are not students,

there are 15 professional researchers, 5 professional artists, 3 teachers, 3 office workers, 2 business owners, 2 salespeople, 1 professor, 1 massage therapist and a few whose professions are unspecified. The age distribution, skewed toward youth, reflects the collegiate community. Education levels are very high for the same reason. Profession is heavily slanted toward life-sciences researchers and students, reflecting the community and the nature of the studies. While many of the subjects with whom we work show a keen and enduring interest in participating, such interest is not likely predictive of anything atypical regarding the results stemming from their presence in a study.

Compared to the U.S. population (potential repellent users), our sampling frame tends to under-represent blacks and over-represent Asians. It is also younger and better educated. Based on review of the scientific literature regarding individual differences in repellent performance and attractiveness to mosquitoes, we conclude that those deviations from the ideal frame will not influence the results' representativeness, or their generalizability to the greater population. Lastly, because our Volunteer Database cohort is comprised of individuals who regularly spend time in outdoor settings (and thereby may have relatively frequent encounters with biting arthropods), this group is probably appropriate for insect repellent users in general.

9.1.6.2. Initial Recruitment Process:

In recent years, our Volunteer Database has grown through people who initiate contact with Carroll-Loye Biological Research. Those individuals learn of our work from persons who have worked with us; we do not direct or actively encourage that process. In those initial contacts, the prospective subjects typically have prior knowledge of our work and its general purpose, and what their fellows have experienced during prior studies. Each individual in the database has requested that we contact him or her in the event that test subjects are needed for insect repellent efficacy testing.

About half of our subjects are present or past University of California, Davis graduate and undergraduate students, and postdoctoral researchers, in life sciences programs. Students who directly depend on the Principal Investigator for employment or for scholastic purposes are not eligible to participate. Those who will serve as untreated control subjects are limited to experienced technical personnel, who are screened with the same exclusion criteria as are other subjects, and have additional inclusion requirements.

Two or more candidate subjects believed to meet the inclusion criteria will be asked if they are willing to consider serving as untreated control subjects. All such subject currently in our Volunteer Database have participated as treated subjects in at least three previous repellent efficacy trials and thus have observed procedures for untreated controls. They are informed during initial recruitment that the Study Director will discuss with them the relative risks of participating as an untreated (versus treated) subject in greater detail during the consenting process. It is emphasized that participation as an untreated control, while construable as an indication of the Study Director's assessment of their personal experience and ability, in no way alters their right to withdraw from the study at any time.

9.1.6.3 Screening of Candidate Subjects:

All such potential participants are screened or re-screened for suitability for each test in a private, one-on-one conversation with the Study Director. Some former subjects have been excluded from mosquito repellent testing, for example, because they surpassed the upper age limit when the health risks of West Nile fever were statistically more serious. The Exclusion Criteria (see §9.1.2, above) are exercised by asking each candidate to address them in the interview with the Study Director. It is explained to female candidates that pregnancy will be assessed directly on the test day. Untreated control subjects are recruited first, so that candidate individuals who wish not to serve as c ontrols do not face the option of being excluded from the entire study.

For candidate untreated control subjects, the practices to be followed during the field study are reviewed in detail. The relative probability of receiving a bite, compared to a treated subject, is discussed in relation to the precautions inherent in the study design, and to the required behavior for untreated control subjects. Optionality for serving in this role is emphasized. The Study Director encourages candidates to ask questions and ask for clarification at any time during the interview and in all activities that follow. To candidates who pass screening, the Study Director describes the test's purpose, as well as necessary procedures and expected comportment, in plain language (in English). Candidates are then asked if they would like to retire from consideration. If they wish to remain in consideration, it is emphasized that they may withdraw from the test at any time during the test without penalty to their compensation. This freedom is especially re-emphasized in cases in which considerable effort or expense has been required to include a subject (e.g., travel to a distant site), to discourage the conception that that effort or expense creates any added obligation in the subject.

Candidates are given copies of the State of California Department of Pesticide Regulation *Experimental Subject's Bill of Rights* (appended) to read in the presence of Carroll-Loye personnel. They are also given a copy of the IRB-approved consent form to read. The amount and form of compensation are described. They are again encouraged to ask any questions about the test, which may include understanding its purpose more fully, understanding risks and discomforts more fully, and understanding treatment and compensation for injury more fully. While the majority of our subjects have worked with us on an occasional basis for a number of years, we encourage them to seriously evaluate their interests and concerns about participation each time. We ask them not to sign on immediately, but to give the situation due consideration (normally at least one day, sometimes less for those who have participated in multiple prior studies). Because most of the volunteers are researchers and/or have advanced degrees in the life sciences, or work directly with or otherwise regularly encounter mosquitoes in infested habitats, we regard their

motivations and decisions to participate as being well-considered and well-informed. Accordingly, we normally accept their decisions to participate if they so choose to following due consideration. Nonetheless, the Study Director retains the final right to refuse participation to any candidate.

9.1.7 Identification method and records retention:

Subjects will initially be identified by first and last name, and assigned a unique number for purposes of this study. Individual data will be entered into the computer for retention and analysis with reference to individual number, not name. Records relating individual names to individual numbers will be retained separately. The Study Director will retain records indefinitely. Subjects may obtain their own records from the Study Director.

9.1.8 Enrollment of alternate subjects and its relation to individual privacy:

We will enroll 3 more subjects than are required to meet our sample size. All subjects will be informed during the consent process that on the day of testing, a small number of subjects may be designated as alternates and sent away after being compensated for coming to the test site. Alternate subjects may return later to replace subjects that initiate testing but withdraw before useful data are generated. They also serve as insurance against any enrolled subjects who fail to appear.

The possibility that any subject may be designated as an alternate will assist in protecting the privacy of any subject that must withdraw in or near the presence of other subjects at the start of the test day (i.e., before treatment and testing begins), for reasons such as a positive pregnancy test result, or for any other personal circumstance.

9.2 Blinding of Study:

None

9.3. Study Material Administration:

Experienced personnel will administer study materials to each subject. Test products will be applied volumetrically to the skin surface from a small syringe, and spread on the site as evenly as possible with one fingertip in a surgical glove, using a light rubbing motion. Skin surfaces to be treated are first cleansed with water and a fragrance-free detergent soap, rinsed with a 35% ethanol-in-water solution, then towel-dried.

9.4 Subject Consent:

Written subject consent is an inclusion criterion.

9.5 Stop Rule and Medical Management:

Specific adverse reactions in subjects to the test materials are not anticipated based on low acute and chronic toxicity, as well as the research design to minimize exposures, and the training of subjects to aspirate landing mosquitoes before they probe or bite. Because the products are topical, technical personnel will monitor, and subjects will self-monitor, for allergic and irritant skin reactions, particularly redness, edema, itching or pain, and report any such reactions to the onsite technical personnel. Any subject showing adverse skin reactions will immediately stop participating. The treated skin will be gently washed with clean water and mild soap to remove the test product, and the area will be gently dried with a clean towel. The subject will be removed from further exposure to mosquitoes.

On the testing day, a physician who has read the protocol and discussed the research with the Study Director will be on call. In unlikely event of a Type 1 allergic reaction (anaphylaxis), we will call 911 by cellular or satellite telephone and cooperate as instructed with emergency personnel. We will be prepared to instruct emergency personnel how to reach our site via multiple routes. In addition, we will personally transport affected persons to the nearest hospital if so advised by emergency personnel. There is

sufficient redundancy in personnel that in such a case, subjects remaining at the study site will still receive appropriate technical, scientific and safety guidance.

All subjects are asked to contact the Study Director and a physician of their own choice at any time should they develop a rash (a delayed hypersensitivity reaction) within 48 hours of the conclusion of the test day.

The risk of mosquito-associated health risks is likewise regarded as very low due to the complementary precautions outlined herein. However, the Study Director will assess the skin condition of affected subjects should any bites inadvertently occur during efficacy testing. In addition, subjects will be asked to make contact with the Study Director at any time should they have health concerns relating to their participation in the efficacy testing.

As part of medical management, the Study Director will record all benign and adverse health observations.

9.6 Subject training for research with mosquitoes:

Approximately 1 week to 1 day before repellent efficacy testing, subjects will be trained by technical personnel in handling mechanical aspirators and observing mosquitoes in the laboratory. Subjects will be shown how to turn on and manipulate the aspirator to capture mosquitoes by a technician who first demonstrates the following procedure, which subjects then emulate: Two laboratory-reared, disease-free female mosquitoes are released in a cage. A small area (less than half) of the forearm is uncovered and exposed in the cage, with no insect repellent applied. Subjects learn how to watch a mosquito approach and land on the arm, how to detect a mosquito's intention to bite, and how to quickly remove LIBing mosquitoes with the aspirator. A technician will be present to instruct and guide throughout; mosquitoes will not be exposed to more than one subject before being destroyed. This 'hands-on' experience will assist subjects in collecting data accurately and handling mosquitoes safely during the repellent efficacy trial. It is detailed in a training document appended to this protocol.

10 TEST VARIABLES AND THEIR MEASUREMENT:

10.1 Variables to be Measured:

Subject forearm and lower-leg surface area.
Subject self-dosing behaviors.
Weight of test materials delivered to the surrogate skin (gauze) dosimeters.
Number of mosquito Landings with Intent to Bite (LIBes) on the treated surface.

10.2 General Considerations:

Dosimetry data collection may be conducted on subject arms, legs or both. Which limbs are used depends on whether efficacy testing, which will follow dosimetry, is to be conducted with repellents sprayed on arms, legs or both. That determination will be made in advance of the dosimetry study, based on the behavior of the mosquitoes present at the chosen field study sites.

10.3 When Variable will be Assessed:

Dosage will be calculated on the basis of surface area of the limb skin that is treated. Measurements to calculate that surface area will be made on each subject in advance of applying the test materials.

Self-dosing behavior will be measured prior to Test Day 1.

In efficacy testing, subjects will record any Landings with Intent to Bite (LIBes) as they occur. Data are recorded in 1-minute exposures at 15-minute intervals. The time at which a treatment's application is completed is recorded as t_0 ('time zero'). The time between application of test materials and the initiation of exposure will be measured. Subjects will practice removing mosquitoes exhibiting LIBes before the field test.

10.4 Procedures for Assessing Variable:

10.4.1 Limb dimensions and surface area:

The term 'limb' refers to the forearm and the lower leg. The surface area of each limb is computed as the average of 4 evenly spaced circumferences (2 peripheral, 2 central) of the forearm (elbow to wrist) or lower leg (back of knee to ankle) multiplied by the length of treatment area.

10.4.2 Familiarization with, and subject use, of the spray apparatus:

Variable assessment will involve a 2-step process, namely subject familiarization with the spray apparatus, followed by dosage measurement.

Subjects will practice applying the test material to their own limbs, following the procedure detailed in the Training Materials appendix, which a researcher will review for subjects before practice commences. That material explains, in simple language intentionally scripted as redundant (to emphasize the work's structure), the goals of this behavioral part of the study, describes the partnership between subject and technician in dosimetry data collection and details the procedures to be conducted.

10.4.3 Spray Sampling:

Spray Sampling is the procedure by which the spray is subsampled with patch dosimeters. Dosimeters of known surface area will be placed on subjects' limbs to intercept a portion of the spray applied to the arm. By weighing dosimetry patches before and after treatment, the mass of the intercepted material can be calculated. The spray delivery systems will also be weighed before and after each application.

Spray sampling will be conducted according to the procedure appended under Training Materials.

10.4.4 Lotion sampling:

The amount of lotion applied to limbs will be quantified in a series of 3 applications analogous to the Spray Sampling above. However, dosimeters are not required, nor are the extensive practice sessions. The amount applied is the weight difference in the dispensing tube before and after application.

10.4.5 Equipment Used to Assess Dosimetry Variables:

Passive dosimeters are 2.5-cm wide strips of Nexcare™ Co-Flex™ cohesive flexible bandage. They are applied to limbs in the manner of 'bracelets.'

Each test limb will be treated 3 times. Each subject will therefore use 12 bracelets per limb for dosimetry.

Bracelets will be weighed before and after treatment on a traceably calibrated Sartorius H51 balance (measurement increment 0.0001 g, 30 g capacity). Test material containers will be weighed before and after dispensing on a traceably calibrated Sartorius GC 2502 (measurement increment 0.001 g, 500 g capacity).

10.4.6 Repellency and LIBes:

Repellency is assessed in the field. Preparatory training of the subjects to recognize and remove mosquitoes that Land with Intent to Bite (LIBe) contributes to subject safety. Subject safety is also enhanced by brief periods of intervallic exposure, and by careful dosing and application.

Subjects will have approximately 1 hour of training and practice in observing foraging mosquitoes and catching them off their own arms in a laboratory cage, using an aspirator. A researcher will first demonstrate the procedure using his or her own arms, and will be present to instruct and guide each subject throughout the exercise. Subjects will be shown how

to place both arms in a screen cage and to turn on the aspirator using the switch on the handle. One mosquito will be released in the cage. A small area (less than half of the forearm) will be uncovered, with no insect repellent applied. Subjects will be instructed to carefully watch the mosquito as it flies in the cage, to observe the mosquito as it lands on the skin, and to watch to see if its needle-like mouthparts are placed against the skin. Once a mosquito lands on the skin, places its mouth against the skin and stops walking, subjects will immediately attempt to catch the mosquito in the plastic nozzle of the aspirator. They may practice as many times as they wish with additional mosquitoes, and the researcher will be certain that the use of the aspirator is correct. After several captures of single mosquitoes, a maximum of 2 mosquitoes will be placed in the cage. 2 LIBing mosquitoes may be readily captured after little practice. 2 represents the maximum number of mosquitoes that may LIBe on limb before the exposure stopping rule is reached (below), so the cage exercise with 2 mosquitoes is highly appropriate.

The mosquitoes used for this training are laboratory-reared, disease-free *Aedes aegypti*. The source colony of *Aedes aegypti* was established from eggs collected in Northern Thailand. F_1 adults were tested by Vero cell (African green monkey kidney, *Cercopithecus aethiops*) plaque assay for possible transovarial infection of viruses. Typically, 20 females from subsequent generations are tested annually, and no infection has been detected in the 3+ years since this colony was established. Individual mosquitoes will not be used for more than one subject.

Before a repellent is applied, subjects will be guided to wash the lower arms and/or legs with mild, fragrance-free soap, rinsing them with a spray of ethyl alcohol (35% in water), then drying the limbs with a clean towel. A technician will then apply the test material to a forearm or lower leg of each subject, providing even, complete skin coverage. The amount of repellent to be applied to any limb will be calculated in advance for each subject. The dosing rate will be the product of the subject's limb surface area multiplied by the grand mean (mean of subject means) rate calculated

in the dosimetry data analysis for the test material. Each subject will therefore be dosed at the same rate, even if their voluntary individual application rates might otherwise differ from the grand mean. The time of application is recorded for each subject. Applications should be made as closely together in time as possible.

Treatments may be applied at the field site or shortly before travel to the field site. Because it is well documented that Picaridin repellents typically give several hours of protection, applications may be made up to 3 hours in advance of the first exposure period if that reduces the probability of subjects needing to withdraw due to exhaustion before receiving a confirmed LIBe. In order not to inflate recorded protection times due to such 'pre-treatment,' any subject treated more than 1 hour in advance of initial exposure who receives a confirmed LIBe within the first 5 exposures, will have his or her limb withdrawn from the study and another limb treated instead. Exposures of the second treated limb will begin at the next exposure period, in order to produce a replacement estimate of Complete Protection Time. All treated limbs are monitored to minimize abrasion with clothing from the time of application.

At the field site, subjects and researchers will gather in an area free of biting mosquitoes. Subjects are instructed not to leave this area until guided by a researcher.

The technicians and other researchers who will assist subjects during the test will be introduced or reintroduced to the subjects. Subjects are instructed to call on them whenever they have questions. Each subject is given and must wear a head net, Tyvek coveralls, latex, nitrile or vinyl gloves in their size. Each subject is also given a mechanical aspirator with which to remove any mosquitoes that land on treated skin and attempt to bite (LIBe) once formal exposures begin. A researcher will remind subjects about how to identify LIBes and when and how to operate the aspirator. Subjects will be further instructed about protecting

themselves from mosquito bites during the test, and about reporting when a mosquito lands on repellent-treated skin.

Treated subjects will be partnered into groups of 2. A researcher will then guide subjects into the area of the field site in which mosquitoes are active. For a 1-minute period, members of a partner pair will watch their own exposed limbs and those of their partner for landing mosquitoes. A technician will advise subjects when this 1-minute period begins and ends. During exposure, subjects will immediately remove any LIBing mosquitoes from exposed skin with the aspirator. They may also use the aspirator's plastic nozzle or a finger to interrupt any mosquito even more quickly. Partners will assist each other in removing mosquitoes as needed.

At the end of the 1-minute exposure period, subjects move away from the area with mosquito activity and take shelter in a shade/screen house nearby. Partners will assist each other in covering the treated skin with the protective garments' sleeve or leg. To reduce abrasion of the treated skin by shifting the sleeves/legs of the protective garments, subjects may leave the skin uncovered between exposure periods if they immediately enter a protected site (e.g., the shade/screen house) and if the Study Director determines that they may do so without risk of uncontrolled additional exposure to mosquitoes. Each subject will report the number of mosquitoes that attempted to bite their own treated skin during that 1-minute period; a technician will record this information on a data sheet. For perspective, note that in a typical test of a reasonably effective repellent, dozens of '0' LIBe values will be recorded for each '1' or '2.' In other words, during most exposure periods, potentially for the first several hours, subjects do not experience close contact with mosquitoes. The probability of eventual direct contact, if any occurs before the cessation of exposure due to darkness or subject withdrawal, increases at a slow rate.

Stopping Rule: Subjects are instructed to immediately cover exposed skin with the protective clothing provided if more than 1 LIBe occurs during a 1-minute exposure period.

Similarly, if subjects receive a LIBe and recall receiving another during either of the 2 previous exposure periods, they are to ask their data-recording technician to verify that recollection from the data record. If verified, the subject is instructed to immediately cover the limb (as specified above).

Ambient LIBe pressure will be measured by experienced, untreated personnel from continuous exposure of a single limb during 1-minute periods commencing once every 15 minutes, beginning at the onset of data collection, concurrent with treated subjects. Such negative control subjects are attended by 2 assistants who use mechanical aspirators, switched on throughout the exposure period, to remove all mosquitoes that LIBe before biting commences. If mosquitoes are too abundant to permit ready aspiration, the controls may protect the exposed limb as soon as a LIBe occurs.

10.4.7 Forms for Retention of Source Data:

Dosimetry data will be recorded on two data forms. 'Landing with Intent to Bite' (LIBe) data will be recorded on a field repellency data form. Data forms are appended.

10.4.8 PCR Virus Assay:

Mosquitoes collected while attempting to bite control and treated subjects will be held in vials labeled with site, subject number, date and time, and placed in portable coolers at approximately 0°C. After completion of the field site testing they will be transferred to a laboratory freezer at Carroll-Loye (ca. -10°C), which will kill them. Dead mosquitoes will be held on ice for identification using a stereomicroscope and taxonomic key. They will the be hand-delivered cold to the University of California Center for Vector-borne disease. There we will run multiplex RT-PCR assays for West Nile Virus, Western Equine Encephalitis, and St. Louis Encephalitis. These three organisms, while rare, are the most likely to cause disease if vectored to a

person by a mosquito bite. With this approach, we anticipate screening 50-100 mosquitoes for the three viruses. The mosquitoes will be screened individually. The goal of this assay is not to measure the minimum infection rate (0.5/1000 is a common rate of epidemiologic interest, for which 40 pools of 50 mosquitoes each is a standard sample). Instead, our goal is to determine whether any of our subjects have come into contact with a pathogen-bearing mosquito. We will alert all subjects to be aware of flu-like symptoms should any positive mosquitoes be detected.

10.5 Study Facility:

Dosimetry data collection will take place in the main laboratory building and on the terrace of Carroll-Loye Biological Research in Davis, CA.

11 DATA ANALYSIS:

11.1 Experimental Unit:

The individual subject will be the experimental unit.

11.2 Replicates per Treatment:

For dosimetry, there will be 10 treated subjects. For efficacy testing, there will be 10 subjects treated with the test material and 2 serving as untreated controls, at each of 2 sites.

11.3 Statistical Methodology:

Statistics will be computed with SAS's JMP software, Version 5.0.1.2 (SAS Institute, Cary, NC).

11.3.1 Dosimetry:

Dosage will be calculated per square centimeter of skin. The amount of test material delivered to each dosimeter set in each trial will be calculated as:

weight after application – weight before application

The **total captured** by all treated dosimeters per trial will be calculated by adding the mass changes in all 4 dosimeters together, then subtracting or adding, respectively, any total weight gain or loss in the paired control dosimeters.

The **proportion covered** of the total limb surface area by the dosimeters is:

$$\frac{\text{Surface area of a set of 4 dosimeters}}{\text{Surface area of the limb}}$$

The estimated **dosage per trial** is:

Total captured x 1/proportion covered

Subject means and standard deviations will be calculated for all measures of dosimeter weight changes as well as application behaviors (distance from nozzle to skin, number of pump actuations). We will use subject dose means for the test material to calculate the dosing grand mean (± SD). That mean, expressed as repellent weight per unit skin surface area, will be converted to volume and used to determine individual subject doses in the field repellency test. To accomplish that, the test material's specific gravity will be used to convert the dosage weight data to volumes, prepared for each subject on the basis of their skin surface area.

Subject effects on dosing behavior will be examined with nonparametric tests for *n*- sample independent cases (Kruskal-Wallis tests). In multiple regression analysis, the average amount of test material intercepted by each subject's dosimeters, as well as dosing per unit of skin surface area, will be examined in relation to the distance

from nozzle to skin, limb size and the number of times the pump was actuated. The relationship between dosing behavior and dosage will also be examined with Spearman-rank correlation tests.

11.3.2. Repellency:

Field tests are conducted with large populations of arthropods. This permits the analysis of the replicates (data by subject) as independent values. The hypothesis that the test material will significantly reduce the number of mosquitoes LIBing on treated versus untreated skin is not the focus of this study. The focus is to compute, for each test material, a reasonable estimate of mean and standard deviation for the duration between application and repellency breakdown sufficient such that two mosquitoes LIBe on a subject within a half-hour period. That pattern is here assessed at a resolution of 15 minutes. The untreated limbs serve to monitor whether the ambient biting pressure remains at or above the EPA standard.

Complete Protection Time (CPT) is measured as the length of time from initial application to the first confirmed LIBe. A confirmed LIBe is a LIBe followed by another LIBe within 30 minutes. For example, a LIBe at 90 minutes followed by another at 135 minutes is not confirmed, but a third LIBe at 150 minutes would confirm that at 135 minutes, giving a CPT of 135 minutes.

CPT measured in this way will yield a single time value for each subject. Mean CPT will be calculated across all 10 subjects, and will be presented with standard deviation and 95% confidence interval information. Ambient LIBing pressure as measured by untreated subjects will be tabulated by individual and exposure period. Mean LIBing pressure will be calculated as the number of LIBes received per untreated control subject and per period and span of exposure.

The decision to calculate means, standard deviations and 95% confidence intervals is based on the requirements for

such estimates in the EPA draft repellent efficacy testing guidelines (1999; OPPTS 810.3700). While EPA staff have indicated at recent HSRB meetings that those guidelines remain under development, they are the de facto standards at present. Accordingly, despite stark statistical weaknesses in making such estimates for samples as small as, e.g., 6 subjects, for consistency with acting standards, we include them. Note that no normalizing data transformations are appropriate in their estimation. Further, as no statistical comparisons are planned, there are no other contexts for normalizing repellency data in the proposed study. To partially ameliorate the shortcomings, our chosen sample size is 10 subjects, which will improve precision in estimating product performance. This sample, which is larger than that traditionally required by US EPA, is implemented at considerable expense to the study sponsor, but is consistent with suggestions from HSRB advisors to EPA.

To further improve the utility of the data set, we propose to use Kaplan-Meier estimates of the survival function of repellency with time since application (Complete Protection Time). Kaplan-Meier analyses provide median estimates with substantially reduced error estimates compared to means and standard deviations; in particular, they are much less sensitive to data censoring. Moreover, they do not rely on assumptions of data normality.' Combining a much larger sample with the Kaplan-Meier estimate of repellent survival improves our ability to estimate the true temporal performance function of test materials in the population.

12 STUDY LOCATION(S):

Field sites are in or adjacent to California's Central Valley or in Southern California (depending on season). Test site information will be provided to EPA once it is clear when testing will be permitted, since seasonality influences the availability of test arthropods on both regional and local scales.

13 QUALITY ASSURANCE:

A separate, professional Quality Assurance Unit (QAU) will inspect the study. The QAU will report to the Study Director. Protocol Review and Comments must take place before data collection commences. In-Life Inspection must include observing the measurement and recording of key variables by subjects and researchers. In addition, the Final Report will be audited for completeness and accuracy. A QAU Statement will address compliance and noncompliance or any omissions in auditing. Findings from the In-Life Inspection and the Final Report, as well as the QAU Statement, will be transmitted to the Study Director and to the Sponsor Monitor.

14 PERSONNEL:

14.1 Investigator (Study Director):

Dr. Scott Carroll

14.1.1 Address:

Carroll-Loye Biological Research
711 Oak Avenue
Davis, CA 95616

14.1.2 Telephone:

530-297-6080
530-297-6081 (Facsimile)

14.1.3 Training and experience of investigator:

CV on file with Carroll-Loye Biological Research

14.2 Study Monitor:

Charlie Duckworth
Division Vice President, Home & Garden R&D

14.2.1 Address:

Spectrum Brands, Inc

13260 Corporate Exchange Dr.
Bridgeton, MO 63044

14.2.2 Telephone:

314-683-2753, 314-254-5907 (Facsimile)

14.3 Quality Assurance Unit:

Dr. William Donahue

14.3.1 Address:

Sierra Research Laboratories
5100 Parker Road
Modesto, CA 95357

14.3.2 Telephone:

209-521-6380

14.3.3 Training and experience of QAU:

CV on file with Carroll-Loye Biological Research

15 AMENDMENTS AND DEVIATIONS TO THE PROTOCOL:

Protocol amendments or deviations will be reviewed by the Study Monitor and the Study Director. Any changes that may affect the health or safety of study participants must be approved the Study Director, the State of California Department of Pesticide Regulation and the approving IRB. The amendments, deviations and any adverse events will be documented in the Study Director's final report. Documentation will include a description of the change, the reason for the change and the effect of the change on the conduct and outcome of the study.

16 PROTOCOL APPROVAL SIGNATURES:

Scott P. Carroll, Ph.D.
Study Director

13 July 2007
Date

Charlie Duckworth
Sponsor Monitor

7/13/2007
Date

INDEPENDENT INVESTIGATIONAL REVIEW BOARD INC.
Your Advocate for Clinical Research Participants

Kim Lerner
Chairman

Anita McSharry, R.N.
President

DATE: July 17, 2007

TO: Scott P. Carroll, PhD
Principal Investigator

FROM: Kim Lerner, Chairman or
Anita McSharry, Vice-Chairman
Independent Investigational Review Board, Inc.

SUBJECT: Approval Clinical Research Protocol dated: 7/16/2007
- Informed Consent Form Treated Subjects (Ver. 7/17/2007)
- Site Questionnaire
- The Experimental Subject's Bill of Rights
- Informed Consent Form Untreated Subjects (Ver. 7/17/2007)
- Administrative Letter dated 7/17/2007

PROTOCOL: (SPC-001) EFFICACY TEST OF PICARIDIN-BASED PERSONAL INSECT REPELLENTS WITH MOSQUITOES UNDER FIELD CONDITIONS

The Independent Investigational Review Board, Inc. is an institutional review Committee structured in compliance with the regulations of the Food and Drug Administration contained in the Code of Federal Regulations (2ICFR 50 and 56 and 45CFR 46) and is in compliance with the International Conference of Harmonization (ICH) Good Clinical Practice (GCP) guidelines for IRB/IECs.

At the meeting held on July 17, 2007, the Committee reviewed and unanimously approved the Research Protocol, the Investigator, Informed Consent Form Treated Subjects, Informed Consent Form Untreated Subjects, Administrative Letter and The California Experimental Subject's Bill of Rights for the above noted research study. The Site Questionnaire was reviewed and unanimously accepted.

The Informed Consent Form Treated Subjects and Informed Consent Form Untreated Subjects is unanimously approved as revised. The Committee recommended that changes be made to the Informed Consent Forms. The approved Informed Consent Forms are identified as Version 7/17/2007 and stamped, "Approved 7/17/2007". The Informed Consent Form contains all regulatory required consent elements. The Experimental Subject's Bill of Rights is stamped "Approved 7/17/2007".

The study has been approved for a 12 month period. At the end of this time, you are required to provide the Independent Investigational Review Board with a written progress report and completed Informed Consent Form for this research and obtain

approval for continuing the research. Changes to the protocol or use of non-approved recruitment materials cannot be initiated without IIRB review and approval.

In the event of any serious adverse events, significant deviations from the protocol or problems in the research, written notice to the Independent Investigational Review Board is required. Please provide this reporting to the above-noted address so that appropriate follow-up will be initiated.

Thank you for your cooperation.

KI/AMS/yc:rr

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

Any person who is requested to consent to participate as a subject in a research study involving a medical experiment, or who is requested to consent on behalf of another, has the right to:

1. Be informed of the nature and purpose of the study.
2. Be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be used.
3. Be given a description of any attendant discomforts and risks reasonably to be expected from the experiment.
4. Be given an explanation of any benefits to the subject reasonably to be expected from the experiment, if applicable.
5. Be given a disclosure of any appropriate alternative procedures, drugs, or devices that might be advantageous to the subject, and their relative risks and benefits.
6. Be informed of avenues of medical treatment, if any, available to the subject after the experiment if complications should arise.
7. Be given an opportunity to ask any questions concerning the experiment or the procedures involved.
8. Be instructed that consent to participate in the study may be withdrawn at any time, and the subject may discontinue participation in the medical experiment without prejudice.
9. Be given a copy of a signed and dated written consent form when one is required.
10. Be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision.

_____ _____

Signature of Subject Date

_____ _____

Signature of Witness Date

APPROVED BY
Independent IRB

_____ 7/17/07

Signature Date

INFORMED CONSENT AUTHORIZATION TO PARTICIPATE AS A RESEARCH STUDY SUBJECT

Title of Study: (SPC-001) EFFICACY TEST OF PICARIDIN-BASED PERSONAL INSECT REPELLENTS WITH MOSQUITOES UNDER FIELD CONDITIONS

Principal Investigator: Scott P. Carroll, Ph.D.
Carroll-Loye Biological Research
711 Oak Avenue
Davis, CA 95616
(530) 297-6080

Site of Investigation: _____
_____

Sponsor: Spectrum Division of United Industries Corporation

Participant's Name: _____

You are being asked to participate in a research study. Your participation is voluntary. The information in this Informed Consent Form explains the study. You will receive a copy of this form, and you may take it home to think about before making your decision. If you have any questions or do not understand anything in this form, please ask the Principal Investigator to explain any words or information you do not clearly understand.

NATURE AND PURPOSE

Carroll-Loye Biological Research is conducting this research study in order to develop effective mosquito repellents. Many people are interested in having new and better insect repellents available to them. The insect repellents that we will study were developed with improved formulations of the ingredient Picaridin, which is relatively new to the U.S. market. More studies are needed to determine how well such new insect repellents work.

The purpose of the study is to test how well this insect repellent, in lotion and pump spray formulations, works outdoors against mosquitoes. The formulations have similar concentrations of Picaridin (5-15%) as products already being sold. The information gained from the study will assist in developing these repellents for commercial marketing. During the study, we will first measure how much insect repellent subjects put on their own arms and legs during a visit to the study laboratory. On a later date, we will go to a field site to test the insect repellents

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Initials: _____
Date: _____

against mosquitoes in nature. You may be asked to participate in one or in both parts of the study.

The sponsor, Spectrum, has contracted Carroll-Loye Biological Research to conduct the study. Scott Carroll, Ph.D., of Carroll-Loye Biological Research is the Principal Investigator (Study Director) in charge of the study.

SUBJECT SELECTION

You have been offered an opportunity to participate in this research study because you read and speak English, consider yourself to be in good physical condition and are 18-55 years old. If you are a female of child-bearing potential, you cannot be pregnant or breastfeeding.

Up to about 58 volunteers will complete this research study. A few more subjects will be enrolled than are needed in order to make up for anyone who is unexpectedly unable to participate once testing begins. If more subjects are present than are needed for any part of the test, you may be asked not to participate, but will instead be an 'alternate subject' who may be contacted to participate later if needed. If you are designated as an alternate, you will be compensated for your participation up to that point and for your inconvenience.

STUDY INTRODUCTION AND DURATION

Schedule of visits and time required to participate in the study

Activity	Visit 1 (2-30 days before the field test)	Visit 2
1. Orientation and Dosage visit	X	
2. Field study visit		X
Total time	2-2.5 hours	8-14 hours

You will be given a training manual and will have a chance to review it and to read along with the instructions.

Visit 1 for Orientation and determining dosage

Within 30 days before the field study visit, you will meet with a researcher to perform orientation activities for the repellent study. The researcher will tell you more about what you will experience while participating and what is expected of you and you will sign this consent form. You may also work with a researcher to determine how much insect repellent you will apply. Completing these measurements will take 1.5-2 hours.

You will also be shown how to use a handheld mosquito-catching device called an aspirator. These devices resemble flashlights, except that they have a small electric fan and suction tube rather than a light bulb. You will carry one of these devices with you during the field study. During this visit, you will also practice

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Signature 7/17/07 Date

Initials: _____
Date: _____

removing mosquitoes from a small area of your arm with the aspirator. This training and practice will take about 15 minutes to a half-hour. The total time for Visit 1 activities will be about 2-2.5 hours.

Visit 2 for the Field Test against Mosquitoes

The study will also require one visit to the site of the field study. The field site visit will most likely require approximately 10 hours of your time. However, it may require as few as 8 hours (including travel time) or as many as about 14 hours, depending on how long the repellents remain effective. Bathrooms are available, and meals, drinks and snacks will be provided. There is a small chance that weather conditions will require that the test be canceled or rescheduled. The Principal Investigator will inform you in a timely manner if that happens.

The Principal Investigator may also ask if you would like to participate in a second field test of these products, using the same procedures as in the first test, on a later date. You may refuse to participate in additional testing without penalty to your compensation.

STUDY PROCEDURES

Study Design

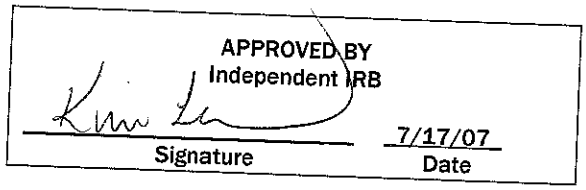
The study will test one lotion and one pump spray. You will have an amount typical of what people commonly use applied to your forearms or lower legs. Two experienced subjects will also participate to record the activity of mosquitoes by exposing their own arms or legs without repellent. Experienced subjects are pre-qualified by the Principal Investigator, and designated before the field test begins. You will not be asked to expose untreated skin and should avoid doing so.

If you are a female, you will perform a pregnancy test using an over-the-counter (OTC) pregnancy kit prior to the start of each of your study visits. Your test results will be verified by a female technician that is qualified to make that determination. If you are pregnant, you will not be allowed to participate in the study. Information regarding your pregnancy test results will be kept in confidence.

Procedures

Visit 1

At the laboratory, a researcher will measure the length and circumference of your forearm and/or lower leg. If you are participating in this part of the study, you will then practice using the product to decide how you best like to apply it and how much you would apply to your forearm or lower leg in order to have thorough and even coverage. The researcher will answer any questions you have about the application. Once you have a method you are satisfied with, you will wash your arms and/or lower legs with soap and water and dry them with a towel. The researcher will then ask you to apply an amount of the repellent product to your



Initials: _____
Date: _____

skin that you think gives complete and even coverage. We will use the amounts you and other subjects apply in this part of the study to determine how much repellent people normally apply.

You will also spend 15-30 minutes practicing catching mosquitoes in a laboratory cage, using an aspirator. You will be shown how to place both arms in a screen cage and turn on the aspirator using the switch on the handle. Two mosquitoes will be released into the cage. A small area (less than half of your forearm) will be uncovered, with no insect repellent applied. You will carefully watch the mosquitoes as they fly inside the cage. Once they land on your skin, you will watch carefully to see if they place their needle-like mouths against your skin. A researcher will be present to instruct and guide you. You may carefully move your arms to get better views and access to the mosquitoes. Once you observe a mosquito mouth touching your skin, you will immediately attempt to catch the mosquito in the plastic nozzle of the aspirator. The researcher will first demonstrate the procedure to you using his or her own arms. You may practice as many times as you wish, and the researcher will be certain that your use of the aspirator is correct. The mosquitoes used for this training are reared in the laboratory and free from diseases.

Visit 2

Before the field testing, the subjects and researchers will gather in an area that is free of biting mosquitoes. You should not leave this area until instructed by a researcher.

You will be given an aspirator to remove any mosquitoes that land on your treated skin and attempt to bite you once the test begins. A researcher will show you again how to operate it. You will also be introduced to the technicians and other researchers who will assist you during the test. You will be instructed to call on them whenever you have questions about using the aspirator, protecting yourself from a mosquito or reporting a mosquito that lands on repellent-treated skin.

Before the repellent is applied, a technician will guide you in washing the lower arms and/or legs with mild, low-fragrance soap, rinsing them with a spray of 35% ethyl alcohol, then drying them with a clean towel. A technician will then apply insect repellent to your forearm or lower leg to give even, complete skin coverage. The amount of repellent applied on any one arm or leg will be no more than about ¼ teaspoon. You will also be given protective coveralls and gloves to prevent bites on other parts of your arms and legs, plus a head net.

After you have had the test repellent applied, the Principal Investigator or one of his technicians will guide you into the area of the field site in which mosquitoes are active. You and a partner will watch your own exposed arms or legs and

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Signature 7/17/07 Date

Initials: _____
Date: _____

those of your partner for mosquitoes that land during a one-minute period. A technician will let you know when the one-minute period begins and ends. If any mosquitoes land and attempt to bite the repellent-treated skin, you will remove them immediately with the mosquito catcher. If at any time you have difficulties using the mosquito catcher, you should push the mosquito from your skin with the catcher's plastic nozzle. You may also use your finger to brush any mosquito aside. If you brush a mosquito aside, watch carefully because it may quickly return to your skin. You will report the number of mosquitoes that attempted to bite your own treated skin during the one-minute period when asked by a technician who will record it on a data sheet. Every 15 minutes, a project leader will announce the beginning of the next one-minute period for testing the treated skin and watching for mosquitoes attempting to bite it. If more than one mosquito attempts to bite you on your treated skin during one of the one-minute periods, or if one mosquito attempts to bite in two of three consecutive exposure periods (that is, 15 or 30 minutes apart), you should cover the skin and not expose it again.

RESTRICTIONS

- You must not be a student or employee of the Principal Investigator.
- You must not be hypersensitive (allergic) to mosquito bites.
- You must not be sensitive to any of the test product ingredients.
- You must regularly spend time in outdoor settings.
- You must not have used repellents within a day prior to the start of the study.
- You must not use perfumed products after 9 p.m. the night before and throughout the tests.
- You must refrain from smoking or consuming alcoholic beverages after 9 p.m. the night before and throughout the tests.
- You must wear specified protective clothing during mosquito testing.

RISKS / DISCOMFORTS

If at any time you feel ill, inform the Principal Investigator (or anyone else who is assisting to direct the study) immediately, and you will be taken to receive medical attention at the nearest healthcare facility. You may also request access to standard first-aid materials (such as bandages, antiseptics and mild antihistamines) and request first-aid assistance at any time. You may remove yourself for any reason from the study at any time. At least one qualified researcher will remain with the other test subjects if other researchers depart with an injured or ill subject.

The repellents will irritate the eyes on contact, and is harmful if swallowed. You may obtain more information about the safety of the repellents by asking a technician at any time. You will be given the Material Safety Data Sheets, which list product safety details similar to those found on commercial product labels.

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Independent IRB
Signature 7/17/07 Date

Initials: _____
Date: _____

In addition, even if you have not previously had a serious skin reaction to a mosquito bite, it is possible that such a reaction could occur if you receive any bites during this study. Swelling, redness and itching near the bite are all symptoms of an allergic reaction to a mosquito bite. You should inform the Principal Investigator or one of his technicians if you are having such a reaction. The first-aid kit at the field site contains treatments to reduce allergic symptoms from bites. Inform the Principal investigator if you are allergic to any nonprescription medicines. At least one technician with current first-aid training will be present during the field test.

In addition, there is a slight possibility that you will contract a disease carried by mosquitoes if you are bitten, such as West Nile virus or equine encephalitis. This test is being conducted in an area in which such viruses have not been detected by state health or mosquito-control agencies for at least a month, so the risk is probably low that any individual mosquito that might bite you carries a disease. In addition, since you are wearing repellent and/or other protective measures, and are carefully watching for mosquitoes that land and try to bite, you are probably at no more risk than you would experience when engaged in normal outdoor activities in a similar rural area at the same time of year.

The U.S. Centers for Disease Control estimates that about 1 in 5 people who become infected with West Nile virus will develop West Nile fever. For up to 2 weeks after the test, be alert for any flu-like symptoms (unusual tiredness or unusually severe headaches, body aches, fever), swollen glands or a rash on the trunk of the body. About 1 in 150 infected people will develop more serious symptoms, including neck stiffness, stupor, disorientation and possibly coma and paralysis.

Most people (about 4 out of 5) who are infected with West Nile virus will not develop any type of illness. Since you will work to quickly remove mosquitoes before they have an opportunity to bite, and since few of the mosquitoes present are likely to carry the virus, your chances of getting West Nile fever or another disease from a mosquito bite are probably extremely small.

If you experience any of the symptoms described above in the month following the field test, you should contact a medical practitioner and inform the Principal Investigator.

To provide additional information about your disease risk during the field test, we will check mosquitoes that land on you and other subjects for the presence of West Nile and similar viruses. That information will be available within one week of the test, and we will inform you both verbally and in writing if any disease organisms were found. Even if you are not aware of receiving any mosquito bites

APPROVED BY
Independent IRB
Signature 7/17/07 Date

Initials: _____
Date: _____

during the field test, if you experience any of the symptoms described above in the month following the field test, you should contact a medical practitioner and inform the Principal Investigator.

PREGNANCY RISKS

The risks to the unborn are unknown and may be hazardous. If you are a woman of childbearing potential, it is important that you do not participate in this study if you are, or if you think you may be pregnant, or if you are lactating.

Pregnancy will be self-checked by each female volunteer on the morning of the repellent test using an OTC test kit provided by the Study Director. Results of each such test will be immediately verified by direct inspection by a female technician trained to make that assessment.

UNKNOWN / UNFORESEEABLE RISKS

In addition to the risks and discomforts listed above, there may be some unknown or infrequent and unforeseeable risks associated with using this product, including allergic reaction or interaction with a medication. You will be informed in a timely manner both verbally and in writing of any new information, findings or changes to the way the research will be performed that might influence your willingness to continue participation in this study.

RESEARCH-RELATED INJURIES

If you are injured as a result of being in this study, a consulting physician who is aware of the study will be contacted immediately by telephone. Medical treatment will be available from a healthcare facility. Carroll-Loye Biological Research will cover the costs of such medical treatment that are not covered by your own insurance or by a third party. If necessary, Carroll-Loye Biological Research will transport you to receive medical attention and pay costs associated with the reasonable and appropriate treatment for any injuries incurred as a result of participation in the study. For further information about this, volunteers should call the Carroll-Loye Biological Research office at (530) 297-6080.

You <u>DO NOT</u> waive your legal rights by signing this form.

TREATMENT ALTERNATIVE

Since this study is not intended to provide any therapeutic or other health-related benefit, your alternative is to not participate in this study.

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Signature 7/17/07 Date

Initials: _____
Date: _____

BENEFITS

There are no immediate benefits to you from your participation. However, by serving as a participant, you may assist in making new insect repellent products available to consumers.

OFFER TO ANSWER ANY QUESTIONS ABOUT THIS STUDY

If you have any questions or problems during this study, or if you think that you may have experienced a research-related injury, you should contact Scott Carroll of Carroll-Loye Biological Research at (530) 297-6080 or (530) 902-8267.

If you have any questions regarding your rights as a research volunteer, please contact Kim Lerner, Chairman of the Independent Investigational Review Board, Inc. toll-free at (877) 888-IIRB (4472) during regular working hours. The Independent Investigational Review Board is a committee established for the purpose of protecting the rights of volunteers in a research study.

COSTS AND REIMBURSEMENT

There will be no costs to you from participating in this study.

For participation in the study, each research study participant will receive a cash payment of $20 per hour. Payment will be made at the end of each visit or whenever you withdraw from the study. If you are designated as an 'alternate subject,' you will be paid for the hours you spent being trained, plus an additional $50 to compensate you for being inconvenienced.

CONFIDENTIALITY

Carroll-Loye Biological Research will retain records of this study indefinitely. You may access your own records by contacting the Study Director however, you might have to wait until the study is over. Representatives from the Sponsor (Spectrum), the U.S. Environmental Protection Agency (EPA), the California Department of Pesticide Regulation and the Independent Investigational Review Board, Inc. (an independent committee that reviewed this study's ethical aspects to help protect the rights and welfare of study participants) may have access to all non-personal information collected in this study. Because of the need to release information to these parties, absolute confidentiality cannot be guaranteed. Any information or reports published as a result of this study will not identify you by name, or by any other personal identification.

STATEMENTS OF UNDERSTANDING

Right to withdraw or removal from study

I understand that I am free to withdraw from this study at any time, and I agree to inform the Principal Investigator immediately if I intend to withdraw. It is understood that my decision to participate in this study or to withdraw from this study will not influence the availability of my future medical care and will involve

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Signature 7/17/07 Date

Initials: _____
Date: _____

no penalty or loss of compensation to which I am otherwise entitled. I may withdraw from this study at any time.

I agree that the Principal Investigator in charge of the study can remove me from this study without my consent for any reason, including, but not limited to:

a. His/her judgment that any condition or circumstance may jeopardize my welfare or the integrity of the study.
b. My failure to follow the instructions of the investigator(s).
c. If the study is stopped by the sponsor and/or Principal Investigator prior to completion.

Consent and signatures

I have read, in a language that I understand well, and understand the information which has been stated above. I have received satisfactory answers to all of the questions that I have asked. I hereby voluntarily consent to take part in this study and to be a research study participant in this study. I do **not** waive my legal rights by signing this Informed Consent Form. I shall receive a copy of the signed Informed Consent Authorization.

Date/Time	**Print** Subject Name	**Sign** Subject Name
Date/Time	**Print** Carroll-Loye Biological Research Representative	**Sign** Carroll-Loye Biological Research Representative

Copy of consent given to subject: (DATE)_____BY (INITIALS) _____

Independent Investigational Review Board, Inc.
Approval: 7/17/07

APPROVED BY
Independent IRB
Signature 7/17/07 Date

Initials: _____
Date: _____

INFORMED CONSENT AUTHORIZATION TO PARTICIPATE AS A RESEARCH STUDY SUBJECT

Title of Study: (SPC-001) EFFICACY TEST OF PICARIDIN-BASED PERSONAL INSECT REPELLENTS WITH MOSQUITOES UNDER FIELD CONDITIONS

Principal Investigator: Scott P. Carroll, Ph.D.
Carroll-Loye Biological Research
711 Oak Avenue
Davis, CA 95616
(530) 297-6080

Site of Investigation: _____
_____

Sponsor: Spectrum Division of United Industries Corporation

Participant's Name: _____

You are being asked to participate in a research study. Your participation is voluntary. The information in this Informed Consent Form explains the study. You will receive a copy of this form, and you may take it home to think about before making your decision. If you have any questions or do not understand anything in this form, please ask the Principal Investigator to explain any words or information you do not clearly understand.

NATURE AND PURPOSE

Carroll-Loye Biological Research is conducting this research study in order to develop effective mosquito repellents. Many people are interested in having new and better insect repellents available to them. The insect repellents that we will study were developed with improved formulations of the ingredient Picaridin, which is relatively new to the U.S. market. More studies are needed to determine how well such new insect repellents work.

The purpose of the study is to test how well this insect repellent, in lotion and pump spray formulations, works outdoors against mosquitoes. The formulations have similar concentrations of Picaridin (5-15%) as products already being sold. Your role will be to serve as a carefully protected, but untreated, control subject. Periodically throughout the test, you will expose skin of your lower arm or lower leg to mosquitoes, with no repellent applied. Assistants will remove the mosquitoes as quickly as possible, normally before you are bitten.

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Independent IRB
Signature 7/17/07 Date

Initials: _____
Date: _____

The information gained from the study will assist in developing these repellents for commercial marketing. During the study, we will first measure how much insect repellent subjects put on their own arms and legs in a visit to the study laboratory. On a later date, we will go to a field site to test the insect repellents against mosquitoes in nature. You may be asked to participate in one or in both parts of the study.

The sponsor, Spectrum, has contracted Carroll-Loye Biological Research to conduct the study. Scott Carroll, Ph.D., of Carroll-Loye Biological Research is the Principal Investigator (Study Director) in charge of the study.

SUBJECT SELECTION

You have been offered an opportunity to participate in this research study because you read and speak English, consider yourself to be in good physical condition and are 18-55 years old. If you are a female of child-bearing potential, you cannot be pregnant or breastfeeding. To be considered as a subject who exposes untreated skin, you must be regarded as competent to do so by the Principal Investigator, must have participated in at least five prior Carroll-Loye repellent efficacy trials, or have participated in at least three such trials and have at least two years of experience as a college life sciences major, or be professionally employed in vector control services.

Up to about 58 volunteers will complete this research study. A few more subjects will be enrolled than are needed in order to make up for anyone who is unexpectedly unable to participate once testing begins. If more subjects are present than are needed for any part of the test, you may be asked not to participate, but will instead be an 'alternate subject' who may be contacted to participate later if needed. If you are designated as an alternate, you will be compensated for your participation up to that point and for your inconvenience.

STUDY INTRODUCTION AND DURATION

Schedule of visits and time required to participate in the study:

Activity	Visit 1 (2-30 days before the field test)	Visit 2
1. Orientation and Dosage visit	X	
2. Field study visit		X
Total time	2-2.5 hours	8-14 hours

You will be given a training manual and will have a chance to review it and to read along with the instructions.

Visit 1 for Orientation and determining Dosage

Within 30 days before the field study visit you will meet with a researcher to perform orientation activities for the repellent study. The researcher will also tell

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Signature 7/17/07 Date

Initials: _____
Date: _____

you about what you will experience while participating and what is expected of you and you will sign this consent form. You may also work with a researcher to determine how much insect repellent you will apply. Completing these measurements will take 1.5-2 hours.

You will also be shown how to use a handheld mosquito-catching device called an aspirator. These devices resemble flashlights, except that they have a small electric fan and suction tube rather than a light bulb. You will carry one of these devices with you during the field study. During this visit, you will also practice removing mosquitoes from a small area of your arm with the aspirator. This training and practice will take about 15 minutes to a half-hour. The total time for Visit 1 activities will be about 2-2.5 hours.

Visit 2 for the Field Test against Mosquitoes

The study will also require one visit to the site of the field study. The field site visit will most likely require approximately 10 hours of your time. However, it may require as few as 8 hours (including travel time) or as many as about 14 hours, depending on how long the repellents remain effective. Bathrooms are available, and meals, drinks and snacks will be provided. There is a small chance that weather conditions will require that the test be canceled or rescheduled. Carroll-Loye personnel will inform you in a timely manner if that happens.

The Principal Investigator may also ask if you would like to participate in a second field test of these products, using the same procedures as in the first test, on a later date. You may refuse to participate in additional testing without penalty to your compensation.

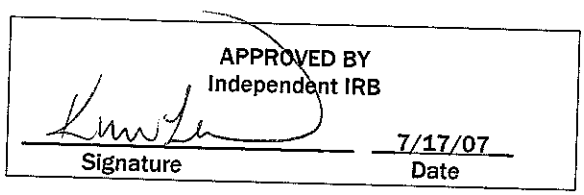
STUDY PROCEDURES

If you are a female, you will perform a pregnancy test using an over-the-counter (OTC) pregnancy kit prior to the start of each of your study visits. Your test results will be verified by a female technician that is qualified to make that determination. If you are pregnant, you will not be allowed to participate in the study. Information regarding your pregnancy test results will be kept in confidence.

Procedures

Visit 1 Dosage determination

At the laboratory, a researcher will measure the length and circumference of your forearm and/or lower leg. If you are participating in this part of the study, you will then practice using the product to decide how you best like to apply it and how much you would apply to your forearm or lower leg in order to have thorough and even coverage. The researcher will answer any questions you have about the application. Once you have a method you are satisfied with, you will wash your arms and/or lower legs with soap and water and dry them with a towel. The



Initials: _____
Date: _____

researcher will then ask you to apply an amount of the repellent product to your skin that you think gives complete and even coverage. We will use the amounts you and other subjects apply in this part of the study to determine how much repellent people normally apply.

You will also spend 15-30 minutes practicing catching mosquitoes in a laboratory cage, using an aspirator. You will be shown how to place both arms in a screen cage and turn on the aspirator using the switch on the handle. Two mosquitoes will be released into the cage. A small area (less than half of your forearm) will be uncovered, with no insect repellent applied. You will carefully watch the mosquitoes as they fly inside the cage. Once they land on your skin, you will watch carefully to see if they place their needle-like mouths against your skin. A researcher will be present to instruct and guide you. You may carefully move your arms to get better views and access to the mosquitoes. Once you observe a mosquito mouth touching your skin, you will immediately attempt to catch the mosquito in the plastic nozzle of the aspirator. The researcher will first demonstrate the procedure to you using his or her own arms. You may practice as many times as you wish, and the researcher will be certain that your use of the aspirator is correct. The mosquitoes used for this training are reared in the laboratory and free from diseases.

Visit 2

Before the field testing, the subjects and researchers will gather in an area that is free of biting mosquitoes. You should not leave this area until instructed by a researcher.

You will be given an aspirator to remove any mosquitoes that land on your untreated skin and attempt to bite you once the test begins. A researcher will show you again how to operate it. You will also be introduced to the technicians and other researchers who will assist you during the test. You will be instructed to call on them whenever you have questions about using the aspirator, protecting yourself from a mosquito or reporting on a mosquito that lands on your untreated skin.

A technician will guide you in washing the lower arms and/or legs with mild, low-fragrance soap, rinsing them with a spray of 35% ethyl alcohol, then drying them with a clean towel. You will also be given protective coveralls and gloves to prevent bites on other parts of your arms and legs, plus a head net.

The Principal Investigator or one of his technicians will guide you into the area of the field site in which mosquitoes are active. You and two other observers will watch your exposed arm or leg for mosquitoes that land during a one-minute period. A technician will let you know when the one-minute period begins and ends. If any mosquitoes land and attempt to bite, the observers or you will

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Independent IRB
Signature 7/17/07 Date

Initials: _____
Date: _____

remove them immediately with the aspirator. If at any time you have difficulties using the aspirator, you should push the mosquito from your skin with the aspirator's plastic nozzle. As soon as the first such mosquito has been removed, immediately cover your exposed skin with the fabric (sleeve or leg) of the coveralls. A technician will record the number of mosquitoes that attempted to bite your exposed skin during the one-minute period (normally 1 or 0). Every 15 minutes, a project leader will announce the beginning of the next one-minute period for exposing your untreated skin and watching for mosquitoes attempting to bite it.

RESTRICTIONS

- You must not be a student or employee of the Principal Investigator.
- You must not be hypersensitive (allergic) to mosquito bites.
- You must not be sensitive to any of the test product ingredients.
- You must regularly spend time in outdoor settings.
- You must not have used repellents within a day prior to the start of the study.
- You must not use perfumed products after 9 p.m the night before and throughout the tests.
- You must refrain from smoking or consuming alcoholic beverages after 9 p.m. the night before and throughout the tests.
- You must wear specified protective clothing during mosquito testing.

RISK/DISCOMFORTS

If at any time you feel ill, inform the Principal Investigator (or anyone else who is assisting to direct the study) immediately, and you will be taken to receive medical attention at the nearest healthcare facility. You may also request access to standard first-aid materials (such as bandages, antiseptics and mild antihistamines) and request first-aid assistance at any time. You may remove yourself for any reason from the study at any time. At least one qualified researcher will remain with the other test subjects if other researchers depart with an injured or ill subject.

The repellents will irritate the eyes on contact, and is harmful if swallowed. You may obtain more information about the safety of the repellents by asking a technician. You will be given the Material Safety Data Sheets, which list product safety details similar to those found on commercial product labels.

In addition, even if you have not previously had a serious skin reaction to a mosquito bite, it is possible that such a reaction could occur if you receive any bites during this study. Swelling, redness and itching near the bite are all symptoms of an allergic reaction to a mosquito bite. You should inform the Principal Investigator or one of his technicians if you are having such a reaction. The first-aid kit at the field site contains treatments to reduce allergic symptoms

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Independent IRB
Signature 7/17/07 Date

Initials: _____
Date: _____

from bites. Inform the Principal investigator if you are allergic to any nonprescription medicines. At least one technician with current first-aid training will be present during the field test.

In addition, there is a slight possibility that you will contract a disease carried by mosquitoes if you are bitten, such as West Nile virus or equine encephalitis. This test is being conducted in an area in which such viruses have not been detected by state health or mosquito-control agencies for at least a month, so the risk is probably low that any individual mosquito that might bite you carries a disease. In addition, since you are wearing repellent and/or other protective measures, and are carefully watching for mosquitoes that land and try to bite, you are probably at no more risk than you would experience when engaged in normal outdoor activities in a similar rural area at the same time of year.

The U.S. Centers for Disease Control estimates that about 1 in 5 people who become infected with West Nile virus will develop West Nile fever. For up to 2 weeks after the test, be alert for any flu-like symptoms (unusual tiredness or unusually severe headaches, body aches, fever), swollen glands or a rash on the trunk of the body. About 1 in 150 infected people will develop more serious symptoms, including neck stiffness, stupor, disorientation and possibly coma and paralysis.

Most people (about 4 out of 5) who are infected with West Nile virus will not develop any type of illness. Since you will work to quickly remove mosquitoes before they have an opportunity to bite, and since few of the mosquitoes present are likely to carry the virus, your chances of getting West Nile fever or another disease from a mosquito bite are probably extremely small.

If you experience any of the symptoms described above in the month following the field test, you should contact a medical practitioner and inform the Principal Investigator.

To provide additional information about your disease risk during the field test, we will check mosquitoes that land on you and other subjects for the presence of West Nile and similar viruses. That information will be available within one week of the test, and we will inform you both verbally and in writing if any disease organisms were found. Even if you are not aware of receiving any mosquito bites during the field test, if you experience any of the symptoms described above in the month following the field test, you should contact a medical practitioner and inform the Principal Investigator.

APPROVED BY
Independent IRB

Signature 7/17/07 Date

Initials: _____
Date: _____

PREGNANCY RISKS

The risks to the unborn are unknown and may be hazardous. If you are a woman of childbearing potential, it is important that you do not participate in this study if you are, or if you think you may be pregnant, or if you are lactating.

Pregnancy will be self-checked by each female volunteer on the morning of the repellent test using an OTC test kit provided by the Study Director. Results of each such test will be immediately verified by direct inspection by a female technician trained to make that assessment.

UNKNOWN / UNFORESEEABLE RISKS

In addition to the risks and discomforts listed above, there may be some unknown or infrequent and unforeseeable risks associated with using this product, including allergic reaction or interaction with a medication. You will be informed in a timely manner both verbally and in writing of any new information, findings or changes to the way the research will be performed that might influence your willingness to continue participation in this study.

RESEARCH-RELATED INJURIES

If you are injured as a result of being in this study, a consulting physician who is aware of the study will be contacted immediately by telephone. Medical treatment will be available from a healthcare facility. Carroll-Loye Biological Research will cover the costs of such medical treatment that are not covered by your own insurance or by a third party. If necessary, Carroll-Loye Biological Research will transport you to receive medical attention and pay costs associated with the reasonable and appropriate treatment for any injuries incurred as a result of participation in the study. For further information about this, volunteers should call the Carroll-Loye Biological Research office at (530) 297-6080.

You <u>DO NOT</u> waive your legal rights by signing this form.

TREATMENT ALTERNATIVE

Since this study is not intended to provide any therapeutic or other health-related benefit, your alternative is to not participate in this study.

BENEFITS

There are no immediate benefits to you from your participation. However, by serving as a participant, you may assist in making new insect repellent products available to consumers.

APPROVED BY
Independent IRB

Signature _____ Date 7/17/07

Initials: _____
Date: _____

OFFER TO ANSWER ANY QUESTIONS ABOUT THIS STUDY

If you have any questions or problems during this study, or if you think that you may have experienced a research-related injury, you should contact Scott Carroll of Carroll-Loye Biological Research at (530) 297-6080 or (530) 902-8267.

If you have any questions regarding your rights as a research volunteer, please contact Kim Lerner, Chairman of the Independent Investigational Review Board, Inc. toll-free at (877) 888-IIRB (4472) during regular working hours. The Independent Investigational Review Board is a committee established for the purpose of protecting the rights of volunteers in a research study.

COSTS AND REIMBURSEMENT

There will be no costs to you from participating in this study.

For participation in the study, each research study participant will receive a cash payment of $20 per hour. Payment will be made at the end of each visit or whenever you withdraw from the study. If you are designated as an 'alternate subject,' you will be paid for the hours you spent being trained, plus an additional $50 to compensate you for being inconvenienced.

CONFIDENTIALITY

Carroll-Loye Biological Research will retain records of this study indefinitely. You may access your own records by contacting the Study Director however, you may have to wait until the completion of the study. Representatives from the Sponsor (Spectrum), the U.S. Environmental Protection Agency (EPA), the California Department of Pesticide Regulation and the Independent Investigational Review Board, Inc. (an independent committee that reviewed this study's ethical aspects to help protect the rights and welfare of study participants) may have access to all non-personal information collected in this study. Because of the need to release information to these parties, absolute confidentiality cannot be guaranteed. Any information or reports published as a result of this study will not identify you by name, or by any other personal identification.

STATEMENTS OF UNDERSTANDING

Right to withdraw or removal from study

I understand that I am free to withdraw from this study at any time, and I agree to inform the Principal Investigator immediately if I intend to withdraw. It is understood that my decision to participate in this study or to withdraw from this study will not influence the availability of my future medical care and will involve no penalty or loss of compensation to which I am otherwise entitled. I may withdraw from this study at any time.

I agree that the Principal Investigator in charge of the study can remove me from this study without my consent for any reason, including, but not limited to:

APPROVED BY
Independent IRB
Signature 7/17/07 Date

Initials: _____
Date: _____

a. His/her judgment that any condition or circumstance may jeopardize my welfare or the integrity of the study.
b. My failure to follow the instructions of the investigator(s).
c. If the study is stopped by the Sponsor and/or Principal Investigator prior to completion.

Consent and Signatures

I have read, in a language that I understand well, and understand the information which has been stated above. I have received satisfactory answers to all of the questions that I have asked. I hereby voluntarily consent to take part in this study and to be a research study participant in this study. I do **not** waive my legal rights by signing this Informed Consent Form. I shall receive a copy of the signed Informed Consent Authorization.

Date/Time	**Print** Subject Name	**Sign** Subject Name
Date/Time	**Print** Carroll-Loye Biological Research Representative	**Sign** Carroll-Loye Biological Research Representative

Copy of consent given to subject: (DATE)_____BY (INITIALS) _____

Independent Investigational Review Board, Inc.
Approval: 7/17/07

APPROVED BY
Independent IRB
Signature 7/17/07 Date

Initials: _____
Date: _____

Limb Measurement Form

Study:

Date:

Subject number:

Data recorder name:

Data recorder signature:

Note: all measurements in cm

			Circumference					
Limb	**Length**	**Length/3[1]**	**Lower (A)**	**Lower-mid (B)**	**Upper-mid (C)**	**Upper (D)**	**Mean circumference[2]**	**Surface area[3]**
Left forearm								
Right forearm								
Left lower leg								
Right lower leg								

[1] For placing dosimeters in pump spray & aerosol studies. 'B' is 1/3 Length from 'A' (wrist/ankle), 'C' is 1/3 Length from 'B' & 'D' (elbow/knee crease).

[2] Sum of the four circumferences measured per limb, divided by 4.

[3] Product of mean circumference and length

Untreated Dosimeter Control Dosimetry Form

Weights of untreated dosimeters before and after placement on limbs

Study: **Date:**

Subject number: **Data recorder name:**

Test article: **Data recorder signature:**

Control trial dosimeters

Arm	Mass before (g)	Mass after (g)
Left		
Right		

Leg	Mass before (g)	Mass after (g)
Left		
Right		

Lotion Dosimetry Form

Study:

Date:

Subject number:

Data recorder name:

Test article:

Data recorder signature:

Left Arm Practice Application		
Trial number	Mass before (g)	Mass after (g)
Practice		

Right Arm Practice Application		
Trial number	Mass before (g)	Mass after (g)
Practice		

Left Arm Sampling		
Trial number	Mass before (g)	Mass after (g)
1		
2		
3		

Right Arm Sampling		
Trial number	Mass before (g)	Mass after (g)
1		
2		
3		

Left Leg Practice Application		
Trial number	Mass before (g)	Mass after (g)
Practice		

Right Leg Practice Application		
Trial number	Mass before (g)	Mass after (g)
Practice		

Left Leg Sampling		
Trial number	Mass before (g)	Mass after (g)
1		
2		
3		

Right Leg Sampling		
Trial number	Mass before (g)	Mass after (g)
1		
2		
3		

Pump Spray Dosimetry Form

Study:
Subject number:
Test article:

Date:
Data recorder name:
Data recorder signature:

Left Arm Practice Application

Trial number	Cm from skin	# pumps to cover	Container before (g)	Container after (g)		
Practice						

Right Arm Practice Application

Trial number	Cm from skin	# pumps to cover	Container before (g)	Container after (g)		
Practice						

Left Arm Sampling

Trial number	Cm from skin	# pumps to cover	Container before (g)	Container after (g)	Dosimeter before (g)	Dosimeter after (g)
1						
2						
3						

Right Arm Sampling

Trial number	Cm from skin	# pumps to cover	Container before (g)	Container after (g)	Dosimeter before (g)	Dosimeter after (g)
1						
2						
3						

Left Leg Practice Application

Trial number	Cm from skin	# pumps to cover	Container before (g)	Container after (g)		
Practice						

Right Leg Practice Application

Trial number	Cm from skin	# pumps to cover	Container before (g)	Container after (g)		
Practice						

Left Leg Sampling

Trial number	Cm from skin	# pumps to cover	Container before (g)	Container after (g)	Dosimeter before (g)	Dosimeter after (g)
1						
2						
3						

Right Leg Sampling

Trial number	Cm from skin	# pumps to cover	Container before (g)	Container after (g)	Dosimeter before (g)	Dosimeter after (g)
1						
2						
3						

Efficacy Dosage by Subject

Study:_____

Test Material:_____ **Specific gravity:_____**

Subject no.	Sex	Limb	Length (cm)	Lower - A	Lower-mid - B	Upper-mid - C	Upper-D	Whole surface (cm^2)	Dose rate gm per cm^2	Dose rate ml per cm^2	Total dose by limb ml	

Surface area = [(A+B+C+D)/4] x Length
Dose rate in g is from dosimety analysis
Dose rate in ml = dose rate in g/specific gravity
Total dose by limb ml = Dose rate ml/cm2 x Surface area

Efficacy dosage by subject.xls

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Test Reference: SPC-001

CLBR Training Manual

§1.c. Practicing and performing dosimetry with a Pump Spray delivery system

A. Goals of exercise

1. Determine your preferred practices for applying ('self-dosing') a pump spray repellent to your arms and/or legs.
2. Assist technicians in measuring the amount of repellent that you apply when using your practices

B. General information

1. A technician will measure the surface area of your forearms and/or lower legs. He or she will introduce you to the repellent and its dispenser
2. You will work in open air, practicing applying the repellent. A technician will help you keep track of your preferred technique.
3. Using small gauze "bracelets" around your limbs to collect samples of repellent you spray on, you will apply repellent with your preferred practices several times. The bracelets will be quickly removed and weighed. You will thoroughly wash your limbs with a gently skin cleaner between each application of repellent.

C. Materials and equipment needed

1. Test materials
2. Latex or vinyl gloves (various sizes)
3. Bracelet dosimeters with nonabsorbent backing
4. Temperature, humidity and wind speed measuring devices
5. Written copy of the procedures for subjects to read
6. Flexible metric rule

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D. Practicing the methods and performing the measurements

Measuring arms and legs[1]:
'Limb' is used to refer to your forearm and/or your lower leg. A technician will measure the distance around your limbs at four evenly spaced places on the forearm (elbow to wrist) and lower leg (back of knee to ankle), and also length of those limbs.

Working with the pump spray and determining your preferred method of applying the repellents:

Your trainer/technician will help to introduced you to how the spray bottle works and how you will determine your preferred methods of applying them. You will read the written procedures that follow here together.

"Read along on your copy of the procedure as the Researcher reads them to you. Ask questions of the Researcher as they occur to you or at any time thereafter. Be sure to get answers to any questions you feel should be answered before proceeding at any step of this work.

This is a study of your behavior in applying spray insect repellents. You may have had experience with applying pump spray products of some kind to your skin before. If you are uncertain about how to use a spray dispenser, be sure to ask the Researcher or one of the technicians. You will each have the opportunity to practice these procedures with the aid of a technician.

Insect repellents function to repel insects from biting the skin. Their effectiveness is influenced by the completeness of their application to the skin surface. Our goal is to determine your preferred method for achieving **full coverage**. At minimum, **full coverage** is defined as a continuous and complete layer of test material. Orienting the limb to light may aid in determining whether full coverage has been achieved. Spray as much as necessary to achieve full coverage.

---

1 **Limb dimensions and surface area (technical details):**
The term 'limb' refers to the forearm and [1]the lower leg. The surface area of each limb is computed as the average of four evenly spaced circumferences (two peripheral, two central) of the forearm (elbow to wrist) or lower leg (back of knee to ankle) multiplied by the length of treatment area. The locale along the limb at which each circumference is taken will be recorded (for later use to place dosimeters) as the distance in centimeters from the distal margin of the site of the most distal circumference site (i.e., at wrist or ankle).

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In these instructions, the act of spraying a repellent on your limb will be termed 'spraying', 'application', or 'dispensing.'

You may work with the spray on your arms, legs, or both. The technician will inform you. Wash your limbs to be tested thoroughly with the provided cleanser and dry with a clean towel. Place new latex or vinyl gloves on each hand, choosing the size that fits you most snugly without being uncomfortably restricting or likely to tear when you put them on.

You will work with a technician who will assist you in measuring and recording your use of a repellent product in a pump spray delivery system.

First, familiarize yourself with the spray mechanism. Any actuation (pushing down on the pump plunger) of the spray must take place out-of-doors. Work at a distance of no less than 6 feet (1.9 meters) from other subjects. Do not dispense the spray at or near your face or anyone else's. Minimize inhalation of airborne spray while working.

Testing will take place out-of-doors during daylight hours at an air temperature (shade) above 10 °C (50 °F) and wind speed below 12 kph (7 mph), with no precipitation. The researcher or a technician will inform you when these conditions are not met and spraying of the repellents will cease until those conditions resume.

Dispense the spray on one limb designated by the technician. By successively moving the spray nozzle closer to and farther from the limb, identify a distance between nozzle and skin that seems most appropriate for effective application to the skin. The technician will measure and record that distance to the nearest centimeter on the provided datasheet.

Have the technician wash and dry the treated limb so that none of the repellent you have applied is visible on close inspection.

Now, using the spray nozzle at or near the distance from the skin that you have just chosen to be effective for application, determine the minimum number of actuations (pumps of the pump spray). Depress the plunger fully each time, and count them aloud beginning with "1, 2, 3 ...." etc. If you partially depress the plunger (rather than fully depress it) in order, e.g., to apply to a small skin area not covered be initial application, report that to the technician as a "half pump." Each partial depression should be so reported as it occurs. If on any given actuation material fails to be delivered, do not count that actuation. If a partial amount is delivered, estimate its volume as 'whole', 'half' or 'none' and report it as such. For 'none', simply resume counting at the next actuation that delivers material to the skin.

Report the count to the technician who will record it on the data sheet. The technician will also assist you in keeping track of whole versus half pumps. Discard your latex gloves, and wash both test limbs (arms or legs) with cleanser and dry them thoroughly with a towel.

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Next, repeat the application procedure and collect the same data for the other limb. In doing so, try to be consistent with your use of the spray apparatus. If you are clear and confident about the distance from the limb that works best, pay enough attention to keep the nozzle in that general range while maintaining a natural delivery as you would use the product under normal personal use. Keep the nozzle aimed at the skin surface, and avoid orienting the containers in any ways that you determine, as you proceed with the trial, to interfere with delivery of the repellent to the skin surface.

Now move on to the **Spray Sampling** exercise described in the next section."

Spray Sampling[2]

Spray Sampling is the procedure by which the spray is "subsampled" with "patch dosimeters". Dosimeters of known surface area will be placed on subject lower limbs. These dosimeters will intercept a portion of the spray applied to the limbs. Be weighing dosimetry patches before and after treatment, the mass of the intercepted material can be calculated. The spray delivery systems will also be weighed before and after each application.

Spray sampling will be conducted according to the following procedure.

"Please read along with the Study Director as he reads aloud the following description of the procedures you will employ in spray sampling. Please be sure to ask questions at any point.

This procedure is very similar to what you have just performed. The main difference is that for spray sampling, a technician will place four narrow rings of plastic-backed gauze around each of your test limbs. The rings are about one inch (2.5 cm) wide. Each of these "gauze bracelets" will be centered on each of the four positions on the limb at which we initially

---

[2] **Equipment Used to Assess the Dosimetry Variable (technical detail):**

Passive dosimeters are 2.5 cm wide strips of 3M Brand Nexcare™ Co-Flex™ self-adhesive roll gauze.

a) Subject number
b) L (for left placement) or R (for right arm placement)
c) Position letter: a (wrist), b (next proximal), c (next proximal), d (elbow)
c) T (for treatment) or C (for control)
d) Replicate number (1, 2 or 3)

There will be eight bracelets per replicate. Each arm and/or leg will be treated three times. Each subject will therefore have a total of twenty-four or forty-eight custom bracelets made and labeled in advance.

Bracelets will be weighed before and after treatment on a traceably calibrated Sartorius H51 balance (measurement increment 0.0001 g, 30 g capacity). Test material containers (pump spray and aerosol) will be weighed before and after dispensing on a traceably calibrated Sartorius GC 2502 (measurement increment 0.001 g, 500 g capacity).

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measured the circumference. These positions may be marked on the skin with small but visible dot using a temporary marker.

The function of the "gauze bracelets" is to capture some of the spray that would otherwise reach your limb as you apply the test products. It is important that you do not alter the way in which you apply the materials in any intentional or substantial way from what you have already determined is your best procedure. The technician will review your results from your previous applications with you to assist you in repeating your general procedure (distance of nozzle to skin, number of spray pumps or aerosol sweeps) as you apply the materials to one of your limbs with the bracelets in place.

The gauze bracelets are narrow in order to minimize the extent to which your sensation of receiving the spray on the limb is changed. Do your best to proceed as if the sensation is not changed. In other words, attempt to avoid spraying additional material onto areas under the bracelets where the sensation of test material on the skin will be different or absent. Do not attempt to spray additional material directly onto a bracelet unless it is within an area that needs additional treatment. Again, attempt to repeat the procedure that you have already developed, and apply the materials "as if the bracelets were not there."

Put a new latex glove on each hand. Spray material onto one limb only. The technician will tell you to which limb to apply spray. You and the technician will collect the same data as previously.

After you have completed spraying, keep both limbs from making contact with any surface. All bracelets will be removed by a technician and taken for weighing.

Discard your gloves, and wash both limbs with cleanser and dry them thoroughly with a towel.

Repeat these procedures until you have made at total of three spray samples for the first limb, and three more for the second limb. If you have completed sampling on, e.g., both arms, the technician may then ask you to repeat the same measurement on both legs. Be sure to discard your gloves, and wash all limbs with cleanser and dry them thoroughly with a towel, including after the last application."

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Test Reference: SPC-001

CLBR Training Manual

§1.a. Observing mosquito landings and learning mechanical aspiration

A. Goals of exercise

1. Learn to determine when a mosquito on your arm is about to bite.
2. Learn to use a "mechanical aspirator" to remove such a mosquito before it bites. Catch at least 10 mosquitoes.

B. General information

1. A technician will show you how to watch mosquitoes that land on you to see if they are about to bite. He or she will then show you how to remove mosquitoes. quickly with a handheld mosquito catching device called a mechanical aspirator
2. You will work with you arms in a screen cage about 1 foot square, with up to two mosquitoes in the cage at one time.
3. You may be bitten by a mosquito while learning to use the aspirator. The mosquitoes were reared in the laboratory and are free from disease.

C. Materials and equipment needed

1. Mosquito cage with entrance stocking
2. Latex or vinyl gloves (various sizes)
3. "Ace" bandage
4. Approximately 12 mature unfed adult female *Aedes aegypti* mosquitoes
5. Mechanical aspirator with charged batteries and collection tube

D. Learning the methods

Spend at least 15-30 minutes practicing observing and catching mosquitoes, working with one or two at a time. Aspirators resemble flashlights except that they have a small electric fan and suction tube rather than a light bulb. You will carry one with you during the field test of the repellent. Your trainer will first demonstrate the method of use and capture. The trainer will then cover your upper forearm with the bandage to protect that area from biting.

Put on gloves. Practice using the switch on the aspirator handle to turn it on, and insert the sucking tube into the cage through the elastic cloth. Then place your arm with the bandage into the cage. About half or your forearm will be uncovered, with no insect repellent. Carefully watch the mosquito as it flies in the cage. Once it lands on your skin, watch carefully to see if it stops walking and places its needle-like mouth against your skin. You may move your arms to get better views and access to the mosquito. Once you observe a mosquito mouth touching your skin, you will immediately attempt to catch the mosquito in the plastic nozzle of the mosquito catcher. You may practice as many times as you wish, with one and then two mosquitoes, and the researcher will be certain that your use of the mosquito catcher is correct.

Spectrum
Division of United Industries
P. O. Box 142642
St. Louis, MO 63114-0642

Material Safety Data Sheet

Complies with OSHA's Hazard Communication Standard, 29 CFR 1910.1200

Hazardous Material Identification System – (HMIS)	
HEALTH – 1	REACTIVITY – 0
FLAMMABILITY – 2	PERSONAL – None

I Trade Name: Cutter Advanced Insect Repellent

Product Type: Insect Repellent Pump Spray

Product Item Number: 53663 **Formula Code Number:** 21-0827

EPA Registration Number	Manufacturer	Emergency Telephone Numbers
121-89	Chemsico Division of United Industries Corporation 8494 Chapin Industrial Drive St. Louis, MO 63114	**For Chemical Emergency:** 1-800-633-2873 **For Information:** 1-800-767-9927 **Prepared by:** C. A. Duckworth **Date Prepared:** Jan. 4, 2005

II Hazards Ingredient/Identity Information

Chemical	%	OSHA PEL	ACGIH TLV
Picaridin CAS # 119515-38-7	7.00	NE	NE
Ethanol CAS #64-17-5/ 977021-81-0	30.00	1000 ppm	1000 ppm

III Physical and Chemical Characteristics

Appearance & Odor: Water-white with an alcohol odor
Boiling Point: NA
Vapor Pressure: NA
Specific Gravity: 1.0
Vapor Density: NA
% Volatile (by vol.): 90%
Solubility in Water: NA
Evaporation Rate: Approximately 1 (Butyl Acetate = 1)
PH: 7.4

IV Fire and Explosive Hazards Data

Flash Point: 87 F (PMCC)
Flame Extension: NA
Autoignition Temperature: N/A
Fire Extinguishing Media: Carbon dioxide, Foam, Dry chemical
Decomposition Temperature: NA
Special Fire-Fighting Procedures: *For Small Fires:* Use Carbon dioxide or dry chemical extinguisher. *For Large Fires:* Use copious amounts of water.
Unusual Fire and Explosion Hazards: Also see Section VII

V Reactivity Data

Stability: Stable
Polymerization: Will not occur
Conditions to Avoid: None
Incompatible Materials: May soften or damage some synthetics such as rayon. May damage leather.
Hazardous Decomposition or Byproducts: None

VI Health Hazard Data

Eye Contact: Causes moderate eye irritation. **First Aid:** Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes then continue rinsing eye. Call a Poison Control Center or doctor for treatment advice. Have the product container or label with you when calling a Poison Control Center or doctor or going for treatment.
Special Notes: **None**
Health conditions Aggravated by Exposure: None known
Ingredients listed by NTP, OSHA, or IARC as Carcinogens or Potential Carcinogens: None

VII Precautions for Safe Handling and Use

Steps to be Taken in Case Material is Released or Spilled:
Combustible material. Remove all possible ignition sources. Soak up with absorbent material. Wash small quantities away with soapy water.

Waste Disposal:
If empty: Do not reuse container. Place in trash or offer for recycling. If partially filled: Call your local solid waster disposal agency or 1-800-CLEANUP for disposal instructions.

Handling & Storage Precautions:
Keep away from heat, sparks, or open flame.

VIII Control Measures

Read and follow label directions. They are your best guide to using this product effectively, and give necessary safety precautions to protect your health.

IX Transportation Data

DOT: Not regulated by DOT (limited quantity exception)
IMDG: Not regulated by IMDG (limited quantity exception)
IATA: Not regulated by IATA (limited quantity exception)

Spectrum
Division of United Industries
P. O. Box 142642
St. Louis, MO 63114-0642

Material Safety Data Sheet

Complies with OSHA's Hazard Communication Standard, 29 CFR 1910.1200

Hazardous Material Identification System – (HMIS)	
HEALTH – 1	REACTIVITY – 0
FLAMMABILITY – 2	PERSONAL – None

I Trade Name: Cutter Advanced Insect Repellent$_1$

Product Type: Insect Repellent towelette

Product Item Number:

Formula Code Number: 21-0827

EPA Registration Number	Manufacturer	Emergency Telephone Numbers
121-90	Chemsico Division of United Industries Corporation 8494 Chapin Industrial Drive St. Louis, MO 63114	**For Chemical Emergency:** 1-800-633-2873 **For Information:** 1-800-767-9927 **Prepared by:** C. A. Duckworth **Date Prepared:** February 1, 2005

II Hazards Ingredient/Identity Information

Chemical	%	OSHA PEL	ACGIH TLV
Picaridin CAS # 119515-38-7	5.75	NE	NE
Ethanol CAS #64-17-5/ 977021-81-0	25.00	1000 ppm	1000 ppm

III Physical and Chemical Characteristics

Appearance & Odor: Fabric towelette saturated with clear colorless Liquid
Boiling Point: NA
Vapor Pressure: NA
Specific Gravity: 1.0
Vapor Density: NA
% Volatile (by vol.): 70%
Solubility in Water: NA
Evaporation Rate: Approximately 1 (Butyl Acetate = 1)
PH: 7.4

IV Fire and Explosive Hazards Data

Flash Point: 87 F (PMCC)
Flame Extension: NA
Autoignition Temperature: N/A
Fire Extinguishing Media: Carbon dioxide, Foam, Dry chemical
Decomposition Temperature: NA
Special Fire-Fighting Procedures: *For Small Fires:* Use Carbon dioxide or dry chemical extinguisher. *For Large Fires:* Use copious amounts of water.
Unusual Fire and Explosion Hazards: Also see Section VII

V Reactivity Data

Stability: Stable
Polymerization: Will not occur
Conditions to Avoid: None
Incompatible Materials: May soften or damage some synthetics such as rayon. May damage leather.
Hazardous Decomposition or Byproducts: None

VI Health Hazard Data

Eye Contact: Causes moderate eye irritation. **First Aid:** Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes then continue rinsing eye. Call a Poison Control Center or doctor for treatment advice. Have the product container or label with you when calling a Poison Control Center or doctor or going for treatment.
Special Notes: **None**
Health conditions Aggravated by Exposure: None known
Ingredients listed by NTP, OSHA, or IARC as Carcinogens or Potential Carcinogens: None

VII Precautions for Safe Handling and Use

Steps to be Taken in Case Material is Released or Spilled:
Combustible material. Remove all possible ignition sources. Soak up with absorbent material. Wash small quantities away with soapy water.

Waste Disposal:
If empty: Do not reuse container. Place in trash or offer for recycling. If partially filled: Call your local solid waster disposal agency or 1-800-CLEANUP for disposal instructions.

Handling & Storage Precautions:
Keep away from heat, sparks, or open flame.

VIII Control Measures

Read and follow label directions. They are your best guide to using this product effectively, and give necessary safety precautions to protect your health.

IX Transportation Data

DOT: Not regulated by DOT (limited quantity exception)
IMDG: Not regulated by IMDG (limited quantity exception)
IATA: Not regulated by IATA (limited quantity exception)

Spectrum
Division of United Industries
P. O. Box 142642
St. Louis, MO 63114-0642

Material Safety Data Sheet

Complies with OSHA's Hazard Communication Standard, 29 CFR 1910.1200

Hazardous Material Identification System – (HMIS)	
HEALTH – 2	REACTIVITY – 0
FLAMMABILITY – 3	PERSONAL – None

I Trade Name: Cutter® Advanced Outdoorsman Insect Repellent

Product Type: Aerosol Insect repellent

Product Item Number: 53667 **Formula Code Number:** 21-0865

EPA Registration Number	Manufacturer	Emergency Telephone Numbers
121-92	Chemsico Division of United Industries Corporation 8494 Chapin Industrial Drive St. Louis, MO 63114	**For Chemical Emergency:** 1-800-633-2873 **For Information:** 1-800-767-9927 **Prepared by:** C. A. Duckworth **Date Prepared:** November 29, 2005

II Hazards Ingredient/Identity Information

Chemical	%	OSHA PEL	ACGIH TLV
Picaridin CAS #119515-38-7	15.00	NE	NE
Ethanol CAS #64-17-5	34.00	1000 ppm	1000 ppm
Isobutane	10.00	NE	NE

III Physical and Chemical Characteristics

Appearance & Odor: Light mist spray with an alcohol odor
Boiling Point: NA
Vapor Pressure: NA
Specific Gravity: 0.88 at 72° F (H_2O = 1)
Vapor Density: 1.6
% Volatile (by vol.) >90%
Solubility in Water: NA
Evaporation Rate: Approximately 1 (Butyl Acetate = 1)

IV Fire and Explosive Hazards Data

Flash Point: 80° F (PMCC) liquid portion
Flame Extension: 12"
Autoignition Temperature: N/A
Fire Extinguishing Media: Carbon dioxide, Foam, Dry chemical
Decomposition Temperature: NA
Special Fire-Fighting Procedures:
For Small Fires: Use Carbon dioxide or dry chemical extinguisher. *For Large Fires:* Use copious amounts of water.
Unusual Fire and Explosion Hazards: Also see Section VII

V Reactivity Data

Stability: Stable
Polymerization: Will not occur
Conditions to Avoid: None
Incompatible Materials: May soften or damage some synthetics such as rayon. May damage leather.
Hazardous Decomposition or Byproducts: None

VI Health Hazard Data

Eye Contact: Causes moderate eye irritation. **First Aid:** Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses if present after the first 15 minutes then continue rinsing eye. Call a Poison Control Center or doctor for treatment advice.
Special Notes:

Health conditions Aggravated by Exposure: None known
Ingredients listed by NTP, OSHA, or IARC as Carcinogens or Potential Carcinogens: None

VII Precautions for Safe Handling and Use

Steps to be Taken in Case Material is Released or Spilled:
Flammable material. Remove all possible ignition sources. Soak up with absorbent material. Wash small quantities away with soapy water.

Waste Disposal:
Do not puncture or incinerate. If empty: Place in trash or offer for recycling. If partially filled: Call your local solid waster disposal agency or 1-800-CLEANUP for disposal instructions.

Handling & Storage Precautions:
Keep away from heat, sparks, or open flame. Exposure to temperatures higher than 130°F may cause bursting.

VIII Control Measures

Read and follow label directions. They are your best guide to using this product effectively, and give necessary safety precautions to protect your health.

IX Transportation Data

DOT: Consumer Commodity, Hazard Class ORM-D (Limited Quantity Exception)
IMDG: Aerosols (Maximum 1 Liter), Hazard Class 2, UN-1950, Packing Group III
IATA: Aerosols, Flammable, Containing Substances in Division 6.1, Packing Group III (Each Not Exceeding 1 Liter Capacity), Hazard Class 2.1, UN-1950, Packing Group III

Spectrum
Division of United Industries
P. O. Box 142642
St. Louis, MO 63114-0642

Material Safety Data Sheet

Complies with OSHA's Hazard Communication Standard, 29 CFR 1910.1200

Hazardous Material Identification System – (HMIS)	
HEALTH – 1	REACTIVITY – 0
FLAMMABILITY – 2	PERSONAL – None

I Trade Name: Cutter Advanced Outdoorsman Insect Repellent[1]

Product Type: Insect Repellent Pump Spray

Product Item Number: 53660

Formula Code Number: 21-0845

EPA Registration Number	Manufacturer	Emergency Telephone Numbers
121-91	Chemsico Division of United Industries Corporation 8494 Chapin Industrial Drive St. Louis, MO 63114	**For Chemical Emergency:** 1-800-633-2873 **For Information:** 1-800-767-9927 **Prepared by:** C. A. Duckworth **Date Prepared:** November 22, 2005

II Hazards Ingredient/Identity Information

Chemical	%	OSHA PEL	ACGIH TLV
Picaridin CAS # 119515-38-7	15.00	NE	NE
Ethanol CAS #64-17-5/ 977021-81-0	35.00	1000 ppm	1000 ppm

III Physical and Chemical Characteristics

Appearance & Odor: Water-white with an alcohol odor
Boiling Point: NA
Vapor Pressure: NA
Specific Gravity: 1.0
Vapor Density: NA
% Volatile (by vol.): 90%
Solubility in Water: NA
Evaporation Rate: Approximately 1 (Butyl Acetate = 1)
PH: 7.4

IV Fire and Explosive Hazards Data

Flash Point: 83 F (PMCC)
Flame Extension: NA
Autoignition Temperature: N/A
Fire Extinguishing Media: Carbon dioxide, Foam, Dry chemical
Decomposition Temperature: NA
Special Fire-Fighting Procedures: *For Small Fires:* Use Carbon dioxide or dry chemical extinguisher. *For Large Fires:* Use copious amounts of water.
Unusual Fire and Explosion Hazards: Also see Section VII

V Reactivity Data

Stability: Stable
Polymerization: Will not occur
Conditions to Avoid: None
Incompatible Materials: May soften or damage some synthetics such as rayon. May damage leather.
Hazardous Decomposition or Byproducts: None

VI Health Hazard Data

Eye Contact: Causes substantial but temporary eye injury. Avoid contact with eyes or clothing. Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, using tobacco or using the toilet. **First Aid:** Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes then continue rinsing eye. Call a Poison Control Center or doctor for treatment advice. Have the product container or label with you when calling a Poison Control Center or doctor or going for treatment.
Special Notes: **None**
Health conditions Aggravated by Exposure: None known
Ingredients listed by NTP, OSHA, or IARC as Carcinogens or Potential Carcinogens: None

VII Precautions for Safe Handling and Use

Steps to be Taken in Case Material is Released or Spilled:
Combustible material. Remove all possible ignition sources. Soak up with absorbent material. Wash small quantities away with soapy water.

Waste Disposal:
If empty: Do not reuse container. Place in trash or offer for recycling. If partially filled: Call your local solid waster disposal agency or 1-800-CLEANUP for disposal instructions.

Handling & Storage Precautions:
Keep away from heat, sparks, or open flame.

VIII Control Measures

Read and follow label directions. They are your best guide to using this product effectively, and give necessary safety precautions to protect your health.

IX Transportation Data

DOT: Not regulated by DOT (limited quantity exception)
IMDG: Not regulated by IMDG (limited quantity exception)
IATA: Not regulated by IATA (limited quantity exception)

Spectrum
Division of United Industries
P. O. Box 142642
St. Louis, MO 63114-0642

Material Safety Data Sheet

Complies with OSHA's Hazard Communication Standard, 29 CFR 1910.1200

Hazardous Material Identification System – (HMIS)	
HEALTH – 2	REACTIVITY – 0
FLAMMABILITY – 3	PERSONAL – None

I Trade Name: Cutter® Advanced Sport Insect Repellent

Product Type: Aerosol Insect repellent

Product Item Number: 53661 **Formula Code Number:** 21-0865

EPA Registration Number	Manufacturer	Emergency Telephone Numbers
121-92	Chemsico Division of United Industries Corporation 8494 Chapin Industrial Drive St. Louis, MO 63114	**For Chemical Emergency:** 1-800-633-2873 **For Information:** 1-800-767-9927 **Prepared by:** C. A. Duckworth **Date Prepared:** November 29, 2005

II Hazards Ingredient/Identity Information

Chemical	%	OSHA PEL	ACGIH TLV
Picaridin CAS #119515-38-7	15.00	NE	NE
Ethanol CAS #64-17-5	34.00	1000 ppm	1000 ppm
Isobutane	10.00	NE	NE

III Physical and Chemical Characteristics

Appearance & Odor: Light mist spray with an alcohol odor
Boiling Point: NA
Vapor Pressure: NA
Specific Gravity: 0.88 at 72° F (H_2O = 1)
Vapor Density: 1.6
% Volatile (by vol.) >90%
Solubility in Water: NA
Evaporation Rate: Approximately 1 (Butyl Acetate = 1)

IV Fire and Explosive Hazards Data

Flash Point: 80° F (PMCC) liquid portion
Flame Extension: 12"
Autoignition Temperature: N/A
Fire Extinguishing Media: Carbon dioxide, Foam, Dry chemical
Decomposition Temperature: NA
Special Fire-Fighting Procedures:
For Small Fires: Use Carbon dioxide or dry chemical extinguisher. *For Large Fires:* Use copious amounts of water.
Unusual Fire and Explosion Hazards: Also see Section VII

V Reactivity Data

Stability: Stable
Polymerization: Will not occur
Conditions to Avoid: None
Incompatible Materials: May soften or damage some synthetics such as rayon. May damage leather.
Hazardous Decomposition or Byproducts: None

VI Health Hazard Data

Eye Contact: Causes moderate eye irritation. **First Aid:** Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses if present after the first 15 minutes then continue rinsing eye. Call a Poison Control Center or doctor for treatment advice.
Special Notes:

Health conditions Aggravated by Exposure: None known
Ingredients listed by NTP, OSHA, or IARC as Carcinogens or Potential Carcinogens: None

VII Precautions for Safe Handling and Use

Steps to be Taken in Case Material is Released or Spilled:
Flammable material. Remove all possible ignition sources. Soak up with absorbent material. Wash small quantities away with soapy water.

Waste Disposal:
Do not puncture or incinerate. If empty: Place in trash or offer for recycling. If partially filled: Call your local solid waster disposal agency or 1-800-CLEANUP for disposal instructions.

Handling & Storage Precautions:
Keep away from heat, sparks, or open flame. Exposure to temperatures higher than 130°F may cause bursting.

VIII Control Measures

Read and follow label directions. They are your best guide to using this product effectively, and give necessary safety precautions to protect your health.

IX Transportation Data

DOT: Consumer Commodity, Hazard Class ORM-D (Limited Quantity Exception)
IMDG: Aerosols (Maximum 1 Liter), Hazard Class 2, UN-1950, Packing Group III
IATA: Aerosols, Flammable, Containing Substances in Division 6.1, Packing Group III (Each Not Exceeding 1 Liter Capacity), Hazard Class 2.1, UN-1950, Packing Group III

Spectrum
Division of United Industries
P. O. Box 142642
St. Louis, MO 63114-0642

Material Safety Data Sheet

Complies with OSHA's Hazard Communication Standard, 29 CFR 1910.1200

Hazardous Material Identification System – (HMIS)	
HEALTH – 1	REACTIVITY – 0
FLAMMABILITY – 2	PERSONAL – None

I Trade Name: Cutter Advanced Sport Insect Repellent$_1$

Product Type: Insect Repellent towelette

Product Item Number: 571 **Formula Code Number:** 21-0845

EPA Registration Number	Manufacturer	Emergency Telephone Numbers
121-93	Chemsico Division of United Industries Corporation 8494 Chapin Industrial Drive St. Louis, MO 63114	**For Chemical Emergency:** 1-800-633-2873 **For Information:** 1-800-767-9927 **Prepared by:** C. A. Duckworth **Date Prepared:** November 29, 2005

II Hazards Ingredient/Identity Information

Chemical	%	OSHA PEL	ACGIH TLV
Picaridin CAS # 119515-38-7	12.00	NE	NE
Ethanol CAS #64-17-5/ 977021-81-0	28.00	1000 ppm	1000 ppm

III Physical and Chemical Characteristics

Appearance & Odor: Fabric towelette saturated with clear colorless Liquid
Boiling Point: NA
Vapor Pressure: NA
Specific Gravity: 1.0
Vapor Density: NA
% Volatile (by vol.): 70%
Solubility in Water: NA
Evaporation Rate: Approximately 1 (Butyl Acetate = 1)
PH: 7.4

IV Fire and Explosive Hazards Data

Flash Point: 83 F (PMCC)
Flame Extension: NA
Autoignition Temperature: N/A
Fire Extinguishing Media: Carbon dioxide, Foam, Dry chemical
Decomposition Temperature: NA
Special Fire-Fighting Procedures: *For Small Fires:* Use Carbon dioxide or dry chemical extinguisher. *For Large Fires:* Use copious amounts of water.
Unusual Fire and Explosion Hazards: Also see Section VII

V Reactivity Data

Stability: Stable
Polymerization: Will not occur
Conditions to Avoid: None
Incompatible Materials: May soften or damage some synthetics such as rayon. May damage leather.
Hazardous Decomposition or Byproducts: None

VI Health Hazard Data

Eye Contact: Causes substantial but temporary eye irritation. **First Aid:** Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes then continue rinsing eye. Call a Poison Control Center or doctor for treatment advice. Have the product container or label with you when calling a Poison Control Center or doctor or going for treatment.
Special Notes: **None**
Health conditions Aggravated by Exposure: None known
Ingredients listed by NTP, OSHA, or IARC as Carcinogens or Potential Carcinogens: None

VII Precautions for Safe Handling and Use

Steps to be Taken in Case Material is Released or Spilled:
Combustible material. Remove all possible ignition sources. Soak up with absorbent material. Wash small quantities away with soapy water.

Waste Disposal:
If empty: Do not reuse container. Place in trash or offer for recycling. If partially filled: Call your local solid waster disposal agency or 1-800-CLEANUP for disposal instructions.

Handling & Storage Precautions:
Keep away from heat, sparks, or open flame.

VIII Control Measures

Read and follow label directions. They are your best guide to using this product effectively, and give necessary safety precautions to protect your health.

IX Transportation Data

DOT: Not regulated by DOT (limited quantity exception)
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IATA: Not regulated by IATA (limited quantity exception)

INDEPENDENT INVESTIGATIONAL REVIEW BOARD INC.

SITE QUESTIONNAIRE

Non-Local Review

Protocol # & Complete Study Title: **(SPC-001) EFFICACY TEST OF PICARIDIN-BASED PERSONAL INSECT REPELLENTS WITH MOSQUITOES UNDER FIELD CONDITIONS**

Principal Investigator: Scott P. Carroll, Ph.D

Sub Investigator(s): None

Please indicate the location where study activities will be performed (where patients will be seen excluding Diagnostics) If more than on location is being used you may attach additional pages.

Site Address: Carroll-Loye Biological Research
711 Oak Avenue
Davis, CA 951616 USA

PI's Mailing Address: _____
(If different) _____

If the study is being conducted at more than one location and information requested differs for each location, please provide separate information for each location.

Regulatory/Study Coordinator: Scott Carroll Phone: 530-297-6080 Fax Number: 530-297-6080

Office Phone: 530-297-6080 24 Hour Phone: 530-297-6080

Please complete the following: You may attach copies of relevant procedures.

1. Is this study federally funded requiring review under HSS standards? X No ☐ Yes

2. How will Study Participants be recruited?
   - ☐ Principal Investigator's Clinical Practice
   - ☐ Referrals from other clinical Practices
   - X Data base of potential Volunteers
   - ☐ Advertising in the community* *(*advertisements Must be approved by the IIRB)*
   - X Other *(please specify):* Word of mouth via Volunteers in data base

3. Will you recruit volunteers from vulnerable study populations? X No ☐ Yes *(please specify below)*
   - ☐ Persons kept in detention
   - ☐ Nursing Home Resident/Elderly
   - ☐ Patients in emergency situations
   - ☐ Persons of limited capacity
   - ☐ Minors
   - ☐ Pregnant women
   - ☐ Illiterate
   - ☐ Other: _____
   - ☐ Members of the Armed Forces
   - ☐ Patients with incurable disease
   - ☐ Unemployed/on Public Assistance
   - ☐ Homeless
   - ☐ Employees (Site or Sponsor, etc)
   - ☐ Disabled

   If yes, describe procedures to be followed (if applicable): Our subjects are mainly University of California–Davis graduate and undergraduate students in life science programs with which the Principal Investigator is associated. Students in his laboratory who depend on him directly for employment or scholastically are not eligible to participate.

4. Do the subjects that you intend to enroll in this study come from any type of ethnic background or cultural environment that might have an impact on their ability to understand that participation in the study is voluntary and refusal to participate or discontinuing their participation will not have any adverse impact on the care that they will receive? No

5. Indicate the approximate demographics of your site's anticipated subject population:
___5___% African American __65__% Caucasian __15_% Hispanics __15__% Asian __<1__% Other

6. Will you be enrolling only subjects who speak English in this study? X Yes ☐ No
If No, Is a "local dialect" or translation needed? Translation needed: ☐ Spanish ☐ Other _____

7. Who will discuss the research study with the volunteer and obtain informed consent (signed informed consent)? *(Check all that apply)*

X Principal Investigator ☐ Sub Investigator ☐ Study Coordinator
Explain consenting procedures: We contact subjects who participated in previous Carroll-Loye repellent efficacy tests by selecting them from our Volunteer Database. At that time interested individuals often ask if one or more of their lab mates or acquaintances can participate as well. All such potential participants are screened or re-screened for suitability for each test in a private, one-on-one conversation held at the office of the Principal Investigator (PI). The Exclusion Criteria (section 9.1.3) are exercised by asking each candidate to address them in the interview with the PI. The PI encourages candidates to ask questions and ask for clarification at any time during the interview and in all activities that follow. To candidates that pass screening the PI describes the test purpose in plain language (in English), and the procedures and comportment to be followed are described in detail. Candidates are then asked if they would like to retire from consideration at that point. If they wish to remain in consideration, it is explained and emphasized that they may withdraw from the test at any time during the test without penalty to their compensation. They are also given a copy of the IRB-approved consent form to read as it is read aloud. The amount and form of compensation is described. They are again encouraged to ask any questions they have about the test, which may include understanding its purpose more fully, understanding risks and discomforts more fully, and understanding treatment and compensation for injury more fully. While the majority of our subjects have worked with us on an occasional basis for a number of years, we encourage them to personally evaluate their interests and concerns about participation seriously each time. We ask them not to sign on immediately but to give the situation due consideration (normally at least one day, sometimes less for those who have participated in multiple prior studies). Because most of the volunteers are researchers and/or have advanced degrees in life sciences, we regard their motivations and decisions to participate as being unusually well considered and well informed. Accordingly, we normally accept their decisions to participate if they so choose following due consideration. Nonetheless, the PI retains the final right to refuse participation to any candidate.

8. Describe the setting(s) where the study will be conducted (ie, private office, clinic, hospital environment) and if the Investigator is required to seek any type of administrative or Corporate approval in order to implement the study:
Private Laboratory owned by Principal Investigator and Field Sites accessed by the PI that are mosquito habitats

*If being done in a Hospital or Outpatient Surgery Center, please provide a copy of that facility's License/accreditation and/or Hospital IRB Waiver Form.

9. Distance between the nearest hospital and research site: 1.8 miles from Laboratory, within 25 miles of field sites.

10. Describe the on-site emergency equipment available for the subjects: First aid kit that includes antihistamines and Epi-pens, skin washing soap and mild dermal detergent, eye wash.

11. How long has the PI been conducting clinical research? ___17_____years ____9_____months

12. Within the past 3 years has the FDA/OHRP audited your site/Principal Investigator? X No ☐ Yes*
**If yes, please provide a copy* of all 483's *and any applicable correspondence.*

13. Has the FDA/OHRP or any State Medical Board ever sanctioned the Principal Investigator? XNo ☐Yes*
**If yes, please provide a summary of the action and applicable correspondence.*

14. Are subject files adequately stored and protected to ensure subject confidentiality, i.e. HIPAA, HIV, etc.? ☐ No* X Yes
**If no, please explain:* _____

15. Does the Principal Investigator, Sub Investigator(s) or any immediate family member have a conflict of interest with the study sponsor, sponsor representatives or other study related entities? X No ☐Yes*
**If yes, please provide explanation:*
_____
_____

Subject Compensation:

Will subject be paid for participation in this study? ☐ No X Yes*
**If yes, please specify the total amount, the amount for each visit and the timing of payment (i.e. at each visit, at the last visit, within 2 weeks of the last visit) in the draft Informed Consent Form.*

Site Specific Informed Consent Form Information

Is there any additional wording needed in the Informed Consent Form? X No Yes*
**If yes, please specify the section and additional wording below.*
Already present in attached draft form.

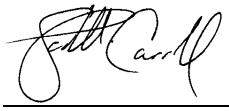
_____

_____

Investigator Acknowledgment

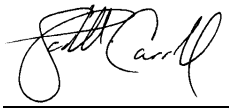
On behalf of all of the investigators listed on page1, I agree that the responses provided on the Site Questionnaire are true and accurate and I agree to notify the Independent Investigational Review Board, Inc. of any changes in the research activities and to report any unanticipated problems involving risk to the research subjects. In addition, I agree not to make any changes in the research without IRB approval. I confirm that study personnel are familiar with the study and that either an Investigator or a study coordinator acting as my designee will orally explain the Informed Consent Form to all prospective subjects before obtaining their signed informed consent. Furthermore, by signing this form I confirm that I agree to conduct the study in accordance with the requirements of the protocol, for which I am seeking approval.

Scott P. Carroll
Print name of individual completing Site Questionnaire



Signature of individual completing Site Questionnaire — Date: 11 July 2007

Scott P. Carroll
Print Name of Principal Investigator



Signature Principal Investigator — Date: 11 July 2007

Please contact the Independent IRB, if you have any questions regarding this questionnaire 954.327.0778

INDEPENDENT INVESTIGATIONAL REVIEW BOARD INC.

Study Specific Instructions

Protocol Title: (SPC-001) EFFICACY TEST OF PICARIDIN-BASED PERSONAL INSECT REPELLENTS WITH MOSQUITOES UNDER FIELD CONDITIONS

Sponsor: Spectrum Division of United Industries Corp.
Contact Info:

Contact/Title	Phone/Fax	email
Scott P. Carroll, Ph.D/Study Director	(530) 297-6080/6080	spcarroll@ucdavis.edu
Mr. Charlie Duckworth Sponsor Monitor	314-254-590	charlie.duckworth@spectrumbrands.com

CRO:
Contact Info:

Contact/Title	Phone/Fax	email

PROGRESS REPORT NOTIFICATION PROCEDURES: (To whom do we send the notice, etc.) Study Director

SPANISH LANGUAGE REQUIRMENTS: (If it is determined that a Spanish language ICF is necessary).

___ Use translations Services though IIRB (Americo Gomez)

___ We will provide our own Spanish Translations

Mailing Instructions: address for Sites do NOT need to be listed – just identify as "sites" (so that we have on file who get copies and who gets originals!)

Originals to: Scott P. Carroll	Sent by: FedEX **X** UPS - USPS
Address: Carroll-Loye Biological Research 711 Oak Avenue, Davis, CA 95616	Account #: 177-484-318
Copies to:	Sent by: FedEX – UPS - USPS
Address:	Account #:

Notes: (include if routine correspondence get copies sent to CRO/Sponsor, sent US Mail, etc.)

Progress Report Information:
To Study Director
Scott P. Carroll, Carroll-Loye Biological Research, 711 Oak Avenue, Davis, CA 95616

Billing Instructions:
To Study Director: Scott P. Carroll

Billing Address: Scott P. Carroll, Carroll-Loye Biological Research, 711 Oak Avenue, Davis, CA 95616

Record of Correspondence between PI and IRB, SPC-001

Date: July 13, 2007
To: "Robert Roogow" <rroogow@iirb.com>
From: Scott P Carroll <spcarroll@ucdavis.edu>
Subject: Initial submission, Protocol SPC-001

Dear Robert,

With this email I submit a new mosquito repellent protocol for the consideration of IIRB.

Thank you very much,
Scott
--
Scott P. Carroll, Ph.D.
Carroll–Loye Biological Research

Date; July 17, 2007
From: "Yesenia Crespo" <ycrespo@iirb.com>
To: <spcarroll@ucdavis.edu>
Subject: SPC-001 and SPC-002

Attached are the approved consent forms. If I can help you with anything else please let me know.
Regards,

Yesenia Crespo
Independent Investigational Review Board INC.

Carroll-Loye Biological Research

711 Oak Avenue Davis, California 95616 Tel (530)297-6080 http://www.carroll-loye.com/

17 July 2007

Mr. Robert Roogow
Independent Investigational Review Board
6738 W. Sunrise Blvd., Suite 102
Plantation, Florida 33313

Administrative Letter, Carroll-Loye Protocol SPC-001

Dear Mr. Roogow,

The formal date for our protocol SPC-001 is 13 July 2007. That date will be reflected throughout, and referenced in any forthcoming revisions.

Thank you very much.

Scott P. Carroll, PhD
Study Director