EFFICACY TEST PROTOCOL LNX-003

EFFICACY TEST OF KBR 3023 (PICARIDIN; ICARIDIN) - BASED PERSONAL INSECT REPELLENTS (20% CREAM AND 20% SPRAY) WITH TICKS UNDER LABORATORY CONDITIONS

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California EPA Review:	Pending
Ammendments:	Pending
Final IRB Approval:	Pending
Standards Applied	U. S. EPA Good Laboratory Practice Regulations (40 CFR 160); 40 CFR 26 subparts K, L and M; FIFRA § 12(a)(2)(P); California State EPA Department of Pesticide Regulation study monitoring (California Code of Regulations Title 3, Section 6710).

SYNOPSIS

This tick repellent study was commissioned by the sponsor to provide efficacy data for purposes of US/EPA registration. The test materials, based on the active ingredient Picaridin, consist of KBR 3023 All-family Insect Repellent Cream (20% Cream) and KBR 3023 All-Family Insect Repellent Spray (20% Pump Spray).

KBR 3023 (Icaridin; Picaridin) is a new generation of synthetic repellent developed as an alternative to DEET. It was developed by molecular modeling

techniques. From more than 800 substances, KBR 3023 showed the best performance regarding efficacy against a variety of arthropods (Boeckh, et al., 1996) and had the most desired attributes regarding safety, low skin penetration, and compatibility with skin, and plastic materials. It was developed by Bayer and is now owned by Saltigo GmbH (Lanxess Group) and in the USA it is handled by Lanxess Corporation (previously a Division of Bayer Corporation).

Icaridin (US EPA Registration Name Picaridin), the current common name, was developed under the Code Name KBR 3023 and the registered trade name Saltidin™ (formerly Bayrepel™) and was sold under the Brand name Autan. The chemical name for Icaridin is 1-PIPERIDINECARBOXYLIC ACID, 2-(HYDROXY-ETHYL), 1- METHYLPROPYLESTER. However, the INCI (International Nomenclature of Cosmetic Ingredients) name was given as HYDROXY METHYL ISOBUTYL PIPERIDINE CARB. The product was submitted to US EPA under the common name Picaridin. However, the common name, Picaridin, was rejected by ISO (International Organization for Standards) as it was not considered a pesticide. The common name Picaridin was also rejected by WHO/INN (World Health Organization/International Non-proprietary Name) but the common name, Icaridin, was accepted by WHO/INN

The study pursuant to this insect repellent efficacy protocol is intended to provide data under the Data-Call-In requirements (EPA Reg. No. 3126-LRN0) of United States Environmental Protection Agency Guideline OPPTS 810.3700.

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1 Justification for Research

1.1 Objective of Research and Endpoints:

The objective is to determine the duration and efficacy of the Test Material(s), when applied at a typical consumer dose, in repelling the following tick species:

Deer tick - *Ixodes scapularis*
American dog tick - *Dermacentor variabilis*

Ticks are certified disease-free laboratory-reared descendents of field caught adults. Methods employed for disease exclusion are described in Appendix 7. Ticks are reared at approximately 25°C under conditions of high humidity and long day length. Laboratory nymphs are active in questing and feeding between approximately 2 weeks and one year post-eclosion (molt). Ticks will typically be between 6 and 12 weeks post-eclosion for testing.

Individual subject dosage will be determined using the standard application rates from the dosimetry completed for related Carroll-Loye Biological Research (CLBR) studies with the Test Material(s).

Efficacy and duration will be measured as Complete Protection Time, or CPT, defined herein as the time between application of test material and the First Confirmed Crossing of an actively foraging tick from the untreated skin surface of a subject's hand 3 cm or more into the treated forearm skin area. A 'First Confirmed Crossing' (FCC) is that which is followed by another within 30 minutes.

The endpoint will be the time of failure expressed as the time of the first confirmed FCC for each subject.

The resulting data set will be suitable for submission to US/EPA to comply with the conditions of the registration.

1.2 Importance of the Research

Insect repellents are commonly used in the United State to reduce both nuisance biting and disease risk. Traditional DEET-based repellents are highly effective, but are cosmetically inferior and relatively more likely to produce mild to serious side

effects. Picaridin-based repellents are cosmetically superior and have a better safety profile. They have been marketed around the world for a decade, but only recently in the US, where they were introduced in 2005. The US Centers for Disease Control (CDC) has acknowledged the existence of substantial consumer interest in new and effective insect repellent products, including the choice of a variety of formulations, delivery systems, and concentrations of active ingredient. Of the three DEET-alternatives currently considered by CDC to have public health value, Picaridin probably has the highest broad-spectrum efficacy. However, few Picaridin products are currently available to US consumers. US EPA has requested new, US-based efficacy data as condition of registration for the test products. The purpose of this study is to provide those efficacy data. The information will also be used in product labeling.

Human subjects are required because they represent the target system for the test material, and sufficiently reliable models for repellency testing have not been developed. Repellent efficacy can only be measured in the presence of biting arthropods. Prevention of tick bites and the reduction of the risks of contracting tick-borne diseases are of substantial interest to U.S. consumers and public health professionals. Thus, there is substantial merit in its further study and the development of new repellent products toward unconditional registration by the U.S. EPA.

1.3 Balance of Risks and Benefits:

The study-associated risks are of five types: exposure to the test materials themselves, exposure to biting arthropods, possible exposure to vectors of arthropod-borne diseases, physical stress from test conditions, and psychological stress associated with a breach in confidentiality concerning pregnancy test results. As described below, subject health and safety are unlikely to be impacted by any study-associated risks during or after the study. Subject health and safety are also safeguarded by medical monitoring, assistance, and management.

1.3.1 Risks from Exposure to Test Material(s)

The repellent active ingredient has a low acute and chronic risk profile (§2), established both through experimentation and through a history of consumer use. 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 (§2).

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.

Subjects with known allergic reactions to insect repellents and common cosmetics are excluded from participating (§3.3.2). Risks associated with inhalation and ingestion would only ensue from serious mishandling by subjects, a scenario that the study methods preclude.

1.3.2 Risks from Exposure to Biting Arthropods

The risk of skin reactions to a bite is reduced by excluding candidate subjects who are aware of having a history of such reaction (§3.3.2). In addition, subjects will be trained to quickly remove any tick that attempts to bite them, before penetration or injection of saliva. Stopping Rules (§4.7.6) and Medical Management practices (§1.3.6) specify removing any treated limb from the study when the repellent begins failing or the subject shows signs of reacting to a bite or to contact with ticks. Subjects will be exposing small areas of treated and untreated skin for a maximum of 24 minutes per hour. Subjects will be teamed with others in a group for mutual observation and experienced technical personnel will be present at all times for assistance.

Within 30 days before repellent efficacy testing, subjects will be trained by technical personnel in handling ticks in the laboratory (Appendix 3). Subjects will learn how to manipulate ticks with fine paintbrushes, place them on their own forearms, observe and quantify tick movement on their arms, and dispose of used ticks. This training will be documented. This ‘hands-on’ experience will assist subjects in collecting data accurately and handling ticks safely during the repellent efficacy trial. This procedure also serves to verify the subject’s attractiveness to ticks in the study.

1.3.3 Risks from Exposure to Disease Vectors

Our laboratory-reared tick populations are certified disease free (Appendix 7). There is no risk of tick-vectored diseases for subjects in our laboratory tests.

1.3.4 Physical Stress in the Test Environment

Physical stresses on subjects are minimized by careful preparation and provisioning. Lab testing environments are temperature and humidity controlled to remain well within human comfort zones. The testing area is maintained free of tripping hazards, and an adjacent rest area is stocked with food, water, and beverages. Seating is provided for all subjects. Private bathroom facilities are also provided on site.

1.3.5 Maintaining Privacy of Pregnancy Test Results

Section 3.3.2 lists the exclusion criterion detailing pregnancy test procedures. Results of a subject's test are only observed by one female CLBR staff technician and never recorded to minimize stress on a female subject testing positive, and minimize the possibility that other staff or subjects may become aware of the results of that test.

1.3.6 Medical Monitoring, Assistance, and Management

Subjects are clearly and repeatedly informed that they may remove themselves for any reason from the study at any time, without penalty to their compensation. 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 7 days of the conclusion of the test day.

On the test day, staff will immediately communicate all subject concerns about health, safety, or comfort to the Study Director for assessment. The Study Director will also assess skin condition of affected subjects should any bites inadvertently occur during efficacy testing, or any subject reports any discomfort in treated areas. Subjects are instructed to inform the Study Director (i.e., the 'Principal Investigator'), or any other staff member if at any time during the study a subject suffers a skin reaction, such as redness, edema, itching or pain, or feels ill. Such subjects will be immediately withdrawn from testing and tick exposure, and medical management will be implemented. When a subject completes the study or is removed for any reason, treated skin areas will be gently washed with clean water and mild soap, rinsed with a 35% ethanol in water solution, then gently dried with a towel to remove test materials.

When medical management is implemented, the Study Director will contact the On-Call physician for the study and comply with the physician's instructions. On the day of testing, a physician who has read the protocol and discussed the research with the Study Director will be on call. Contact information for the nearest medical facilities and maps from the test site to the facilities will be prepared and on file before the day of testing. In unlikely event of a Type 1 allergic reaction (anaphylaxis), we will contact 9-1-1 by cellular or ground-line telephone and cooperate as instructed with emergency personnel. Epi-Pens will be on-site. At least one qualified researcher will remain with the other test subjects if other researchers depart with an injured or ill subject. We will be prepared to instruct emergency personnel on 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.

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.

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

1.3.7 Summary of Risks and Benefits

The combination of technical precautions and natural factors means that the chances that any subject will contract disease, suffer an injury, or suffer a severe reaction from a tick bite are extremely small.

Against these slight risks are balanced substantial and reasonably likely benefits. The principle beneficiary will likely be the Sponsor, for whom new data and new labeling will meet current US EPA registration standards. Because EPA registration requires efficacy data, a test such as that proposed here is the only path toward further product development, greater availability, and increased consumer acceptance of new repellent formulations in the United States. For the general public, tick-borne disease is of growing significance in the United States and around the world where U.S. citizens are active. Moreover, discomfort associated with nuisance biting restricts many work and pleasure activities

2 Test Material(s): Description and Control

The following table summarizes all information about the test material(s) relevant to this study.

Test Materials as referred to in this Protocol:

	Cream 20%	Spray 20%
Test Material name (Picaridin conc.)	KBR 3032 All-Family Insect Repellent Cream (20%)	KBR 3023 All-Family Insect Repellent Spray (20%)
Manufacturer	LANXESS Corporation	LANXESS Corporation
Manufacturing Standards Applied	Good Manufacturing Practice standards, with records available to EPA.	Good Manufacturing Practice standards, with records available to EPA.
Transport	Commercial Courier, express, insulated container	Commercial Courier, express, insulated container
Chain of Custody	Documented	Documented
Specific gravity	0.98	0.96
Delivery system	Lotion	Pump Spray
Active ingredient(s) (%)	Picaridin 20%	Picaridin 20%
Inert ingredients	Proprietary, available to US EPA	Proprietary, available to US EPA
Stability	Stable	Stable
Storage conditions specified	Room temperature, max 30° C (86° F)	Room temperature, max 30° C (86° F)
Storage conditions applied	Locking, closed cabinet at room temperature (19-24°C) protected from light and moisture sources	Locking, closed cabinet at room temperature (19-24°C) protected from light and moisture sources
Description of cosmetic properties	White cream	Clear solution
NOAELs for Picaridin	NOAEL = 200 mg/kg (dermal); 308 mg/kg (oral)	NOAEL = 200 mg/kg (dermal); 308 mg/kg (oral)
Irritation and sensitization class	(Picaridin) No irritant or sensitizing potential	(Picaridin) No irritant or sensitizing potential
Hazard label requirements	Substantial but temporary eye injury. Do not get in eyes. Wash thoroughly with soap & water after handling, returning indoors, and before eating, drinking, chewing gum, or using tobacco. Discontinue use and consult a doctor if irritation or rash occurs; Flammable.	Moderate eye irritation, avoid contact with eyes or clothing, wash thoroughly with soap & water after handling, returning indoors, and before eating, drinking, chewing gum, or using tobacco. Flammable.
Reference materials	Sample labels in Appendix 4, page 52-53 MSDS and Toxicology documents in Appendix 5, page 54-65	

The sponsor is responsible for completing all toxicological screening, compositional analysis, and stability studies for the test material(s) and providing the results to Carroll-Loye Biological Research prior to providing the test material(s) to Carroll-Loye.

3 Research Subjects: Recruitment, Screening, Consent, Privacy

3.1 Candidate Recruitment: Population, Sampling Frame, Representativeness

For reasons of practicality and control, we work with people associated the community in which our business is located (Davis, CA). Davis is a university-dominated community, and so the population demography differs somewhat from non-university communities. Compared to the Population of Concern (the US population - all potential repellent users), our sampling frame tends to under-represent blacks and over-represent Asians. It is also young, well educated, and slanted towards life science researchers and students.

Over time, we have developed a Volunteer Database of individuals who have expressed interest in participating in future repellency tests, provided contact information, and asked us to contact them. Initial recruiting is from this database, then from word-of-mouth of volunteers. The size and composition of the database varies over time as new individuals volunteer and old volunteers move out of the Davis area, but is now typically over 100 individuals, with the following average ethnic (self-identified) and gender distribution (averaged over 3 years):

Male	52%
Female	48%
Caucasian	74%
Asian	12%
Hispanic	7%
African-American	4%
Arabic	3%

In general, about three-quarters of the subjects are age 20-40, with the remainder between 40 and 55. Final composition is not determined until enrollment is completed. The relevant demographics of the participants will be reported.

Carroll (2006) 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 ectoparasite, or likely impact on a repellency trial's data set. Several studies have indicated that individuals differ in attractiveness to mosquitoes, for example, but individual attractiveness rankings shift substantially among parasite taxa. Skin-emanated volatiles influence attractiveness, as do skin temperature and absorption properties; these factors may likewise influence repellent efficacy. Studies of gender, age, race, hair color, complexion, weight, skin moisture, menses (females), hairiness, and sweat have shown only gender to have significant effects on individual attractiveness to mosquitoes. Though studies have shown that sweating increases attractiveness to at least one mosquito species, it is not clear whether individuals that sweat more than others, on average, tend to be more attractive to mosquitoes. Two studies with adequate sample sizes found females to be 25% less attractive to *Aedes* mosquitoes, while the other showed them to be significantly less well protected against *Anopheles* mosquitoes by 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 attempt to enroll similar numbers of males and female subjects.

On the other hand, it *is* clear that conditions of use strongly influence repellent performance. We intentionally test under conditions of light, temperature and humidity conducive to tick foraging behavior. Further, we expose subject individuals as uniformly as possible to the ticks, and have them handle the ticks in ways that minimally disrupt tick behavior. We also monitor subjects 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 arthropod-borne diseases (see above), though the likelihood of contracting the causal agent during a repellent test is very low.

Based on review of the scientific literature regarding individual differences in repellent performance and attractiveness to ticks, we conclude that this study's deviations from the ideal frame will not influence the representativeness of the results, or their generalizability to the greater population. Lastly, because our Volunteer Database cohort is comprised by individuals who regularly spend time in outdoor setting (and thereby may have relatively frequent encounters

with biting arthropods), this group is probably appropriate for insect repellent users in general.

3.2 Candidate Recruitment Procedures

Recruitment for the Repellency Phase begins as soon as the test dates are determined.

Potential candidates are initially contacted by phone from our Volunteer Database and queried about interest and availability. Individuals are chosen using a random number table to choose subject numbers from the database and contacted. During the phone interview, we also inform potential candidates that they are permitted to refer others to us by having them contact us. Recruitment continues until the roster of subjects and alternates is full.

3.3 Candidate Screening

3.3.1 Inclusion Criteria, all subjects

Age: 18-55 years
Sex: Male/female
Race: Any race
Completed Consent Process (§3.4) including providing Written Consent (defined as having read, initialed, dated and signed Informed Consent Form and Experimental Subject Bill of Rights)
Language: Speak and read English

3.3.2 Exclusion criteria, all subjects:

1. Known to be hypersensitive to tick bites or exhibiting hypersensitivity during test
2. Phobic of ticks
3. Known to be allergic to insect repellents or common cosmetics
4. Known to be sensitive or showing sensitivity to any of the test product ingredients after application.
5. Poor physical condition.
6. Unwilling to submit to brief query about personal condition.
7. Use of insect repellent within one day preceding the efficacy test.
8. Unwilling to refrain from use of perfumed products, alcoholic beverages or smoking after 9 PM the evening preceding the efficacy test and throughout that test.

9. Known to be pregnant or lactating. Each female volunteer of child bearing potential will self-check for pregnancy using an OTC test kit provided by a technician on the day of any study visit in which repellent will be applied or in which the subject will be exposed to ticks. Results of each such test will be immediately verified by direct inspection by a female technician experienced in making that assessment. Information regarding pregnancy test results will be kept in confidence. Only volunteers scored as nonpregnant will be allowed to participate.
10. Unable to deliver the test materials or nymphal ticks to own left and right arms.
11. Unable to see nymphal ticks on skin or otherwise effectively monitor them on skin.
12. Student or employee of the Study Director.
13. Does not regularly spend time in outdoor settings.
14. Withdraws from testing before receiving a confirmed crossing, 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.
15. Not attractive to target species.

3.4 Obtaining Subjects' Consent

All candidates are screened or re-screened for suitability for each test in a private, one-on-one conversation with the Study Director, at which time the Exclusion Criteria (§3.3.2) are exercised by asking each candidate to address them. It is explained to female candidates of child bearing potential that pregnancy will be assessed directly on the day of any study visit in which repellent will be applied.

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 that pass screening, the Study Director describes the test purpose in plain language (in English), and the procedures and comportment to be followed are described. Candidates are then asked if they would like to retire from consideration at that point. 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 from a distant site), to discourage the subject from believing that the considerable effort or expense creates an added obligation to participate.

If the candidate indicates he or she wishes to proceed, the Study Director provides a copy of this study's IRB-approved Informed Consent Form (ICF) and State of California Department of Pesticide Regulation 'Experimental Subjects' Bill of Rights' (BOR) for review (Appendix 1). The candidate is also offered their own copy of the protocol itself, and supporting documents (MSDSs, toxicology study results, compositional analysis of the Test Materials, and training documents) for review. In a private session a senior CLBR staff member certified in protecting human research participants by the National Institute of Health (NIH), will read the ICF and BOR documents out loud with the candidate, offering to take questions and answering any that arise. The amount and form of compensation is described.

Candidates 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, or work directly with or otherwise regularly encounter biting arthropods 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 following due consideration. Nonetheless, the Study Director retains the final right to refuse participation to any candidate.

When all screening procedures are complete, the candidate is asked to sign, initial, and date the ICF and BOR for this study, both of which are then cosigned by a NIH certified staff member of Carroll-Loye. The candidate, now a subject, is then asked to complete a contact and emergency medical form

3.5 Protecting Subjects' Privacy

Screening interviews are conducted in private and one-on-one. All written records containing names, contact information, medical information, and signatures are kept in a locked, fire-proof cabinet. Access to these files is restricted to Carroll-Loye staff with the Study Director's permission. All subjects are assigned a unique number to identify them on all data forms and to staff and other subjects during testing activities. Although many subjects interact socially during the tests, and may voluntarily share names or other personal information, subjects are never asked, required, or encouraged to do so. 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 at any time.

We will enroll three 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 who 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.

4 Study Design

4.1 Number of Subjects

In efficacy testing, we will use 10 subjects per treatment. Each subject is a replicate. Ten subjects are two-thirds more than the historical EPA requirement of six subjects. EPA is currently working on more precise guidance on sample size, but that remains forthcoming.

The number of subjects is chosen as a compromise among multiple factors. The goal is to meet regulatory requirements to provide an estimation of the true mean CPT, and so from a scientific standpoint an appropriate response under such circumstances is to increase size, but ethical and economic considerations demand the opposite in the present study, particularly during the efficacy-testing phase.

Importantly, under the historical guidelines, there seem to have been few problems with EPA registering repellents failing to meet their labeled performance specification. Nonetheless, there are clear risks in using a very small sample, and conspicuous among them in this study is that the probability of over-representing subjects inherently unattractive to the target species is rather large. We reduce this risk by confirming subject attractiveness to ticks before they participate in the phase of the test where efficacy data is collected. This should decrease the probability of certain sampling errors substantially.

For calculating EPA-required mean and variance data, estimating the power associated with a given sample size is constrained by three factors, namely, little knowledge of the magnitude of individual CPT values in tick studies, little information regarding the distribution of CPT values in insect repellent studies in general, and, the first consideration notwithstanding, a reasonably high chance that there will be a number of censored values. If a minority of values is censored, and particularly if the range of values is not great (as in related mosquito repellent study LNX-001, MRID 47506401), a sample size of 10 should give excellent estimates of mean, median, and variation around those values, relative to historical standards. Still, 10 is sufficiently small, from both statistical and biological perspectives, that we are confident that we are not oversampling.

EPA has expressed interest in refining how CPT data are assessed and analyzed. We judge that such improvements are best made in the context of a further formalization of how EPA makes its labeling decisions from CPT data sets. The central ideas stem from types of survival analysis. One suggestion is to use, e.g., the time to 25% failure (among subjects) as the labeled protection time (when censoring is not too frequent). Another would require the Agency to specify acceptable Type I error probabilities for estimates of minimum CPTs *exceeding* a specified value. With the latter approach, EPA would also have to judge how to label with respect to the confidence interval around such probability estimates. Like the typical estimation of means and standard deviations, the soundness of such alternative statistical judgments will hinge on the accuracy of assumptions regarding the nature of the population distribution.

Given the success of past practices in application, and our clear improvements in sample size, it is premature for us to suggest further substantial change in how the EPA assesses repellent efficacy data. The basic philosophy, and therefore methodology, of how these data are analyzed should be based on a clear and stable agency strategy regarding the information content of product labels.

4.2 Number of Controls

Each subject simultaneously serves as a treatment and control subject. Ticks are placed on the untreated arm of the subject to determine foraging avidness, then moved to the treated arm. The 'negative control' for efficacy data sets serves to insure that each tick employed in the study is attracted to the test subject before it is used in a repellency challenge. Ticks that fail to meet the questing criterion (§4.8.2.1) are not used against Test Materials. In this way the negative control serves as a pre-screening of the ticks, such that only actively questing ticks are then exposed to the treatments. Based on this manipulation of a standard control design, the crossing rate on the negative control is judged to be 100%.

4.3 Controls for Matrix Materials

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

4.4 Controls with Comparison Materials

There are no comparison materials in this study. Questions of comparison between the Test Materials and other repellents are external to the objective.

4.5 Subject Measurements

We will measure length and circumference of the forearms of subjects. Circumference will be measured at four points (upper forearm, lower forearm, and two equally spaced points in between). This data will be averaged for mean circumference, which will be multiplied by length to calculate surface area. This data will be kept on file for each subject. Subjects will be re-measured bi-annually or if, when asked, they indicate they may have gained or lost weight or muscle mass on their limbs since their measurements were last taken. This practice reduces the frequency of potentially invasive repeated measurement procedures for subjects.

4.6 Standard Dose as Determined by Dosimetry

Dosimetry data are used to determine individual dosing for efficacy testing. Dosing rates are calculated on a per square cm basis. Those rates were obtained in a dosimetry study of each test material in 2007 during our conduct of an earlier study reported as LNX-001 (MRID 47506401).

Dosing Rates, by Test Material

	arms
Cream 20%	*2.51 μl/cm^2
Spray 20%	0.97 μl/cm^2

*We are currently in the process of negotiating with EPA concerning additional dosimetry data collection for the Cream 20% product to augment the data set. Depending on the outcome of the negotiations, we may amend this protocol to include augmented data in the final dosage determination.

The dosing rate for each Test Material is the grand mean rate calculated from 10 subjects (converted from weight to volume by reference to the specific gravity of each test material).

4.7 Efficacy – Components of the test

The efficacy study will consist of one laboratory trial. In each trial, each Test Material will be tested with 10 subjects. The individual subject will be the experimental unit.

Using a mean application rate derived from dosimetry (§4.6), individual dosages will be prepared for each subject volumetrically such that for each Test Material, all subjects receive the same amount of Test Material per unit

skin area exposed. Skin surfaces of both treated and untreated limbs are first cleansed with water and a fragrance-free detergent soap, rinsed with a 35% ethanol in water solution, and then towel-dried. Test Material is dispensed from tuberculin (1 ml) syringes by technicians wearing surgical gloves who apply it to treated subjects by spreading evenly over the area to be treated using one finger in a light rubbing motion. Application of each Test Material is considered a treatment. All treated limbs are monitored to minimize abrasion with clothing or laboratory surfaces from the time of application.

All subjects will be assigned to the treated group, which will be blocked by gender. The treatments will be allocated in sequence ('A', then 'B', then 'A', etc.). Within each gender, the treatments will be allocated at random excepting minor adjustments needed to constrain the numbers treated with a particular Test Material to 10. The treatment each subject receives and the time of application for each subject will be recorded on a data capture form (Appendix 2). Multiple technicians will make the applications, and each application will take only about two minutes to complete, so that subjects receiving 'A', for example, will not be treated on average significantly earlier than those treated with 'B'.

Materials will be distributed among subjects as tabulated below.

Subject	**Cream 20%**	**Spray 20%**
1	Left arm	
2	Left arm	
3	Left arm	
4	Left arm	
5	Left arm	
6	Right arm	
7	Right arm	
8	Right arm	
9	Right arm	
10	Right arm	
11		Left arm
12		Left arm
13		Left arm
14		Left arm
15		Left arm
16		Right arm
17		Right arm
18		Right arm
19		Right arm
20		Right arm

695
696 4.7.1 Blinding of Study
697 Because the treated condition will be evident to researchers, technicians, and
698 subjects, neither staff nor subjects will be effectively blinded. However, within
699 the treated group, the three treatments will be indistinguishable to test subjects
700 and staff based on their physical properties. Accordingly, the three treatments
701 will be coded 'A' or 'B' by a technician. That technician will dispense the test
702 materials so labeled for efficacy test treatments. That technician will not be
703 involved in judging crossing events during efficacy data collection.
704
705 The treatment code key will be recorded in hardcopy by the technician and
706 maintained in a locked file drawer to which only he/she has the key. As a
707 backup, the key will also be recorded in a password protected computer file.
708 For backup access, two technicians will be charged with privately maintaining
709 the password offsite from the laboratory. Technicians will be charged not to
710 reveal the code or the specific identity of test materials at any time during
711 application or data collection, unless needed for medical or legal reasons. The
712 Study Director will retrieve the code key from the technician(s) after the
713 conclusion of data collection.
714
715 This moderate level of blinding security is deemed appropriate for a test in
716 which the performance difference between untreated and treated conditions is
717 unlikely to be ambiguous, and in which the performances of the test materials
718 are not specifically being compared.)
719
720 4.7.2 Target Arthropods
721 Species challenging the repellent in the test are listed in §1.1. We will test
722 repellency against deer tick - *Ixodes scapularis,* and American dog tick -
723 *Dermacentor variabilis*.
724
725 4.7.3 Confirming Tick Foraging Activity
726 To be included in the test on a treated limb, each tick must first meet the
727 crossing criterion on the untreated limb, following the procedure for the treated
728 limb in the same test period (§4.8.2.1).
729
730 4.7.4 Measuring Repulsion
731 The number of crossings on each subject's exposed treated area will be
732 recorded (Appendix 2) as they occur during 3-minute exposure periods
733 commencing once every 15 minutes, beginning at the onset of data collection
734 and ending when the subject receives the First Confirmed Crossing, a stopping
735 rule is invoked for the subject, or the Study Director stops the test for all

subjects. Based on repellency trials of the Test Material(s) against mosquitoes (related study LNX-001, MRID 47506401), we expect the repellents may remain effective for up to 12-14 hours possibly more.

4.7.5 Environmental Conditions – Data

Records (Appendix 2) of presence/absence and general rate/quality data for environmental conditions (temperature, relative humidity, light intensity) will be made at approximately one-hour intervals throughout the course of the laboratory trial.

4.7.6 Stop Rules

All subjects

- Consented duration reached
- Test site becomes unsafe for subjects for any reason
- Foraging pressure falls below threshold needed to challenge the Test Material(s)

Individual subjects

- Subject asks to withdraw
- Subject proves unattractive to target species
- Subject's treated limb receives Confirming Crossings for both target species
- Medical management is invoked for the subject (§1.3.6)

4.8 Sequence of efficacy test procedures

4.8.1 Within 30 days preceding Test Day

Candidate screening and subject consenting and orientation will occur.

4.8.2 1 Day prior to test

Staff prepare laboratory, arranging space in the facility to accommodate all test subjects and staff. A separate area for dispensing food and beverages is prepared and provisioned for subject access throughout the test.

4.8.3 Test Day

Subjects gather at the Carroll-Loye Biological Research laboratory to clean limbs and receive applications. 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. Subjects are also reminded of procedures for the day's test.

The following test procedures are repeated by each subject at designated time intervals until a stop rule (§4.7.6) is invoked.

4.8.3.1 Tick screening for active foraging and repellency challenge

Three 'orientation' ink dots are arrayed longitudinally on both ventral forearms of each subject, at 3 cm intervals. On the treated arm, the first dot is 3 cm distal to the treated area, the second dot marks the threshold of the treated area, and the third dot is 3 cm into the treated area. The untreated limb/limb portion has a spatially identical array of 3 lines for tick activity screening. The first dot, used for placement, insures that ticks are not placed within the treated area and so can detect a gradient of repellent density to which to orient. The second dot serves keep subjects aware of where the treated area begins and serves as a reorientation point for re-marking should either the first or the third dot become obscured.

Subgroups of approximately three subjects are led by a technician in the monitoring of time, ticks, and tick behavior. Every 15 minutes, each subject selects an unused tick and screens it for active questing behavior, repeating until an actively questing tick is identified. The subject then transfers the tick to the treated arm for a repellent challenge.

To initiate a screening or a repellent challenge, a tick is placed on the ventral arm or proximal palm, in the most hair-free portion, at the first (most distal line). Ticks are manipulated with the bristles of a fine artist's paintbrush. Ticks are placed so that they face the elbow. Ticks may be oriented to locomote toward the margin of the treated area with the gentle action of the paintbrush. Forearms should be held from approximately 30° to vertically above the lab bench surface if that increases the propensity of ticks to travel toward the body.

Active questing is verified if a tick travels past the second marker dot in motion towards the elbow on the untreated arm. On the treated arm, a crossing is scored if a tick travels at least 3 cm in a vector toward the elbow into the treated area (i.e., at least as far as the third line) within 3 minutes of beginning to move up the arm from the first line. A repulsion is scored when a tick changes its orientation away from, or parallel to, the margin of the treated area upon approach, or does not cross more than 3 cm toward the elbow within 3 minutes of entering the treated area.

4.8.3.2 Repellency data collection and tick removal

The technician will assist subjects in determining crossing versus repulsion events, and in determining whether a tick may be beginning to bite (an extremely unlikely event), and assisting in removing a tick should a bite occur (no embedding is

anticipated, so removal should be possible with the same small paintbrush). Time is monitored by referring to an electric chronometer with a highly visible display. The technician will record any crossings or repulsions as they occur. Repulsions are normally unambiguous reversals of direction. Subjects lift the tick off with the paintbrush after each assessment is complete. Any brushes that come into contact with a test material are discarded. Used ticks are immediately retired from the study by being transferred from the test arm to a container labeled "used".

4.9 Efficacy – Statistical design and analysis

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

Because all subjects use different ticks, all ticks are used only once, and neither organism interacts directly with conspecifics at the level of the skin and the repellent during data collection, we will analyze data by subject as independent, replicated values. The hypothesis that the test materials will significantly reduce the number of ticks Crossing treated versus untreated skin is not the objective of this study. The objective is to compute, for each test material, a reasonable estimate of mean and standard deviation for the duration between application and sufficient repellency breakdown such that there are two ticks crossings on a subject within a half hour period. That pattern is here assessed at a resolution of 15 minutes.

For each treated subject, we will measure (data form Appendix 2):

- Exposure delay (min) – time between application and first exposure
- Minutes to First Confirmed Crossing (FCC) or end
- Complete Protection Time (CPT) – time between application and FCC

Complete protection time (CPT) is measured as the length of time from initial application to the First Confirmed Crossing (FCC). A FCC is a Crossing followed by another Crossing within 30 minutes. For example, a Crossing at 90 minutes followed by another at 135 minutes is not confirmed, but a third Crossing at 150 minutes would confirm the one at 135 minutes, giving a CPT of 135 minutes.

CPT is measured as a single time value for each subject. Based on the requirements for such estimates in the EPA draft repellent efficacy testing guidelines (1999; OPPTS 810.3700), we will calculate mean CPT across all 10 subjects, with standard deviation and 95% confidence interval information.

Data will be normalized as possible to enhance the value of confidence interval calculations.

As described in §4.74, we anticipate that protection may span up to about 12 hours, and possibly 14 hours or more after application for some subjects. To examine the temporal pattern of failure further, we will employ Kaplan-Meier survival analyses by subject. Kaplan-Meier survival analysis accommodates some data censoring in the event that any subjects withdraw or are withdrawn before failure. In addition, we will estimate the Kaplan-Meier median, and the time until 25% failure, for each test product. In the presence of a high frequency of censoring, median (and mean) values will be underestimated.

Our chosen sample size of 10 subjects will improve precision in estimating test material 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. The resulting data set will be provide values suitable for any additional statistical characterizations of repellent performance that EPA may wish to employ in developing labeling language for the Test Materials.

5 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 technicians. 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 both the Study Director and to the Sponsor Monitor.

6 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 as well as 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.

7. LITERATURE CITED AND SELECTED REFERENCES

Bernard, Donald R., Bernier, U. R., Posey, K. H. and Xue, Rui-De (2002). Repellency of IR 3535, KBR 3023, para-menthane-3,8,-diol, and DEET to Black Salt Marsh Mosquitoes (Diptera: Culicidea) in Everglades national Park). J. Med. Entomology 39(6): 895-899

Boeckh, J.; Breer, H.; Geier, M.; Hoever, F. P.; Kruger, H. W.; Nentwig, G.; Sass, H. Acylated. 1,3-aminopropanols as repellents against bloodsucking arthropods. Pestic. Sci. 1996, 48, 359-373.

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.

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

Constantini, Carlo and Ilboudo-Sanogo, Edith (200-). WHOPES Evaluation of Insect Repellent KBR 3023 in Burkina Faso. Final report for WHO Project V2.181.276

Frances, S.P., Waterson, N.W., Beebe, N.W. and Cooper, R.D. (2004). Field Evaluation of Repellent Formulation Containing DEET and Picaridin against Mosquitoes in Northern Territory, Australia. J. Med. Entomology 41(3): 414-417

Frances, S.P., Van dung, N., Beebe, N. W. and Debboun, M. (2002). Field Evaluation of Repellent Formulations against daytime and Nighttime Biting Mosquitoes in a Tropical forest in Northern Australia. J. Med. Entomology 39(3): 541-544

Luepkes, K. H. Mosquito repellent effects of various formulations based on Bayrepel / KBR 3023 against yellow fever mosquito Aedes aegypti (2005). Unpublished Lanxess report

Yap, H. H., Jahangir, K., Chong, A.C.S., Adanan, C. R., Malik, Y. A. and Rohaizat, B. (1998). Field Efficacy of a New Repellent, KBR 3023, against Aedes albopictus (SKUSE) and Culex quinquefasciatus In a Tropical Environment. Journal of Vector Ecology 23(1): 62-68

Yap, H.H., Jahangir, K. and Zairi, J. (2000) Field Efficacy of Four insect Repellent Products against Vector Mosquitoes in a Tropical Environment. Journal of the Mosquito Control Association. 16(3): 241-244

8 Protocol Approval Signatures

Scott P. Carroll, Ph.D.
Study Director

July 26, 2009
Date

for Stanley C. Oslosky
Stanley C. Oslosky
Head of Regulatory Affairs
LANXESS Corporation

July 27, 2009
Date

G. K. Sangha, Ph. D.
Study Monitor

July 27, 2009
Date

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

Kim Lerner
Chairman

Anita McSharry, R.N.
President

DATE: July 30, 2009

TO: Scott P. Carroll, PhD
Principal Investigator

FROM: Authorized Signatory
Independent Investigational Review Board, Inc.

SUBJECT: Approval Clinical Research;
- Informed Consent Form version 7/28/2009
- Research Protocol version 7/27/09
- Site Questionnaire
- California Experimental Subject's Bill of Rights

PROTOCOL: (LNX-003) EFFICACY TEST OF KBR 3023 (PICARIDIN; ICARIDIN) - BASED PERSONAL INSECT REPELLENTS (20% CREAM AND 20% SPRAY) WITH TICKS UNDER LABORATORY CONDITIONS

The Independent Investigational Review Board, Inc. is an institutional review board structured in compliance with the regulations of the Food and Drug Administration contained in the Code of Federal Regulations (2l CFR 50 and 56, 45 CFR 46, and 40 CFR 26) and is in compliance with the International Conference of Harmonization (ICH) and Good Clinical Practice (GCP) guidelines for IRB/IECs.

At the meeting held on July 28, 2009, the Committee reviewed and unanimously approved the Investigator, Informed Consent Form, California Experimental Subject's Bill of Rights and Research Protocol for the above noted research study. The Site Questionnaire was reviewed and unanimously accepted.

Note: A discrepancy was noted in the protocol related to the screening time period before the test day. On page 7 of the protocol it states within 30 days before repellent efficacy testing, subjects will be trained. However on page 22 section 4.8.1 of the protocol, it states within 60 days preceding test day, candidate screening and subject consenting and orientation will occur.

The Informed Consent Form is unanimously approved. The approved Informed Consent Form is identified as Version 7/28/2009 and stamped, "Approved 7/28/2009". The Informed Consent Form contains all regulatory required consent elements. The California Experimental Subject's Bill of Rights is stamped, "Approved 7/28/2009".

The study has been approved for a 12 month period. Prior to the end of approval on 7/27/2010, 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, Inc. review and approval.

It is the responsibility of the Principal Investigator to submit all unanticipated problems and serious or continuing non-compliance in a timely manner to the IIRB, Inc. For more information on reporting requirements visit www.iirb.com and the Investigator's Guidebook. Please provide this reporting to the above-noted address so that appropriate follow-up can be initiated.

Thank you for your cooperation.

KL/AMS/yc:kk

INFORMED CONSENT AUTHORIZATION TO PARTICIPATE AS A RESEARCH STUDY SUBJECT

Title of Study: LNX-003 EFFICACY TEST OF KBR 3023 (PICARIDIN; ICARIDIN) - BASED PERSONAL INSECT REPELLENTS (20% CREAM AND 20% SPRAY) WITH TICKS UNDER LABORATORY CONDITIONS

Principal Investigator: Scott P. Carroll, Ph.D.
Carroll-Loye Biological Research
711 Oak Avenue
Davis, CA 95616
(530) 902-8267

Site of Investigation: Carroll-Loye Biological Research
711 Oak Avenue, Davis, CA 95616

Sponsor: LANXESS Corporation

Participant's Name: _____

INTRODUCTION

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 request, we will also provide you with a copy of the study Protocol, which details all the procedures of the study, and contains details about product safety. 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 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. 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 cream and pump spray formulations, works against two types of ticks. The information gained from the study will assist in developing these repellents for commercial marketing. During the study, we will test the insect repellents against ticks in a laboratory.

APPROVED BY
Independent IRB
Signature 7/28/09 Date

Initials: _____
Date: _____

The sponsor, LANXESS Corporation, 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 invited to participate in this research study because you are a male or female, 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. Using an over-the-counter (OTC) pregnancy kit supplied by a technician, you will perform a pregnancy test at the laboratory on the day of any study visit in which repellent will be applied or in which you will be exposed to biting insects. Your test results will be verified by a female technician experienced in making that assessment. 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. If you decide to withdraw from the study after taking the pregnancy test you do not need to show a positive result.

RESTRICTIONS

- You must not be a student or employee of the Principal Investigator.
- You must not be hypersensitive (allergic) to tick bites, or phobic of ticks.
- You must not be sensitive to any of the test product ingredients, or allergic to common cosmetics.
- You must regularly spend time in outdoor settings.
- You must be able to see and remove ticks that come in contact with your skin.
- 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. To meet this restriction, you may need to purchase fragrance-free cosmetics prior to the test days. If you do, you will be reimbursed for your expenses.
- You must refrain from smoking or consuming alcoholic beverages after 9 p.m. the night before and throughout the tests.

NUMBER OF SUBECTS PARTICIPATING

Up to about 23 subjects will be enrolled at this single-site 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

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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	Visit 2
1. Orientation visit	X	
2. Field study visit		X
Total time	2-2.5 hours	8-16 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

Within 30 days before the second visit (in which we will test the repellents against ticks), 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 will also be shown how handle ticks on your skin with a small artist's paintbrush. This training and practice will take about ½ hour.

The total time for Visit 1 activities will be about 2-2.5 hours.

Visit 2 for the Tick Repellent Test

The study will also require a second visit to the same laboratory. This second visit will most likely require approximately 12 hours of your time. However, it may require as few as about 4 hours or many as about 16 hours, depending on how long the repellents remain effective. Bathrooms are available, and meals, drinks and snacks will be provided.

STUDY PROCEDURES

Visit 1

At the laboratory, a researcher will measure the length and circumference of your forearm. If you have participated in a Carroll-Loye Biological Research study within the last two years, and were measured for that study, we will use your on-file limb measurements unless, when asked, you indicate that you think you have gained or lost weight or muscle mass on your limbs since the previous measurements were taken.

You will also be given a verbal orientation to the activities of the test day, with an opportunity to ask the researcher questions or share your concerns about any aspect of the research activities.

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Date: _____

At the laboratory, you will spend about 30 minutes practicing handling ticks in the laboratory in preparation for the repellent study. A technician will show you how to catch the ticks, place them on your skin, take them off, and place them in a container. You will practice these tasks several times in order to familiarize yourself with how to handle the ticks carefully and successfully. You will also be trained to recognize tick attachment/biting behavior, which includes cessation of crawling motion and pressing mouth parts against the subject's skin or placing head down against your skin while lifting hindmost legs off of the your skin. If you observe this behavior during the test, you will alert the attending technician, who will remove the tick immediately using a paintbrush or, if needed, tweezers. You may ask the technician for advice on how to handle the ticks at any time while you are practicing. The ticks used for this training are reared in the laboratory and free from diseases.

Visit 2

This is the day of the actual repellent study. You will first be guided to wash your lower arms with mild, low fragrance soap, rinsing them with a spray of ethyl alcohol (mixed at 35% in water), and then drying them with a clean towel. Experienced personnel will then apply repellents to one of your forearms to give even, complete coverage of the skin. The amount of repellent applied on an arm is likely to be no more than about ¼ teaspoon. You will be randomly (like a flip of a coin) assigned to receive either 20% Picaridin Spray or 20% Picaridin Cream. Your other arm will not be treated, but will instead be used to determine whether each tick is active enough to be tested on your treated arm.

During the test, you will be seated at a laboratory table with about six other treated subjects, and a researcher or technician will lead you in handling and keeping track of the ticks, of the time, and of your tick observations. Every 15 minutes, you will test a new tick from one species first on your untreated and then on your treated arm, and report the results to your leader. You will then repeat that sequence with a tick of the other species. Together testing the two ticks will usually take between 5 and 10 minutes to complete. At times you may need to stand so that the ticks may climb upward, which is their preference.

Every 15 minutes a researcher or technician will announce the beginning of the next period for testing the treated skin. You will continue in this way until a tick of each species crosses the repellent in two of three consecutive periods, as long as you are comfortable. There will time for brief breaks to eat and use the bathroom between test periods.

When a technician indicates you are finished with the testing activity, the technician will direct you to discard your gloves and wash any applied skin area to make sure all treatment residues are removed. Using a clean towel each time, wash applied areas with cleanser, rinse with water, dry, then wash with mild alcohol solution (35% ETOH in water) rinse with water, and dry.

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Date: _____

RISKS / DISCOMFORTS

If at any time you feel ill, inform the Principal Investigator (or anyone else who is assisting to direct the study) immediately. 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 without penalty to your compensation. At least one qualified researcher will remain with the other test subjects if other researchers depart with an injured or ill subject.

The cream repellent will cause substantial but temporary injury to eyes on contact. The pump spray repellent will cause moderate irritation to eyes on contact. Both are 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.

If they bite you, ticks can transmit serious diseases, or cause tick paralysis. Ticks require many minutes to bite through the skin, and we do not expect them to attempt to bite you during the study. The artist's paintbrush that we will train you to use to handle ticks will also be used to remove any ticks before they bite or bury in the skin. The ticks have been screened for infectious diseases at the US Centers for Disease Control and have been determined to be free of the pathogens that cause Lyme Disease, Rocky Mountain Spotted Fever, Ehrlichiosis, and Anaplasmosis. Contact a physician and the Principal Investigator if you develop a rash within 7 days after the day of testing. The first-aid kit at the laboratory contains treatments to reduce allergic symptoms. 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 test.

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.

If you are a female subject who is tested for pregnancy, and you test positive, there is some risk of psychological stress from the surprise of the result. Only a single female technician will evaluate the results, and no record will be made of the results, to maximize your privacy by minimizing the small but present risk that other staff or subjects may become aware of the results.

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Date: _____

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, or change the nature of the risks associated with participating.

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 that covers you. 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) 902-8267.

You DO NOT waive any of 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.

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) 902-8267 at any time.

If you have any questions regarding your rights as a research participant, please contact Kim Lerner, Chair of the Independent Investigational Review Board, Inc. at toll free 1- (877) 888-iirb (4472) between 6:00 AM and 2:00 PM, Pacific time, Monday through Friday. You can also contact the Independent Investigational Review Board, Inc. if you would like to report problems in a research study, express concerns, ask questions, request information, or provide input. The Independent Investigational Review Board is a committee established for the

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Date: _____

purpose of protecting the rights of participants in a research study. For more information about your rights and role as a research participant you can visit the Research Participant section of the IIRB, Inc. website at www.iirb.com.

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 $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. Representatives from the sponsor (LANXESS Corporation), 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

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

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

a. His/her judgment that any condition or circumstance may jeopardize your welfare or the integrity of the study.
b. Your 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.

APPROVED BY
Independent IRB
7/28/09
Signature Date

Initials: _____
Date: _____

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 any of my legal rights by signing this Informed Consent Form. I shall receive a copy of the signed Informed Consent Authorization.

Date (MM/DD/YY)	Time	**Print** Subject Name	**Sign** Subject Name

Date	**Print** Carroll-Loye Biological Research Representative	**Sign** Carroll-Loye Biological Research Representative

Copy of signed/dated consent form given to subject on (date)_____ by_____ (initials)

Independent Investigational Review Board, Inc.
Approved: 7/28/09

APPROVED BY
Independent IRB
7/28/09
Signature Date

Initials: _____
Date: _____

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

Any person who is requested to consent to participate as a subject in a research study involving an 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 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 and Experimental Subject's Bill of Rights when one is required.

10. Be given the opportunity to decide to consent or not to consent to an experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision.

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) 902-8267 at any time.

If you have any questions regarding your rights as a research volunteer, please contact Kim Lerner, Chairman of the Independent Investigational Review Board, Inc. at toll free (877) 888-IIRB (4472) between 6AM and 2PM, Pacific Time, Monday through Friday. The Independent Investigational Review Board is a committee established for the purpose of protecting the rights of volunteers in a research study.

_____ _____

Signature of Subject Date

_____ _____

Signature of Witness Date

APPROVED BY
Independent IRB

_____ 7/28/09

Signature Date

CONFIDENTIAL TEST SUBJECT INFORMATION

Name:_____ **Subject #** _____

Address: **Tyvek Size:**_____

Birthdate:_____

Permanent mailing address:
(Where you want tax form 1099 sent) **Handedness:**_____

Contact Information

Home Phone:

Cell Phone:

Email:

Other:

Emergency Contact

Name:

Phone:

Relationship:

Medical Information
(Anything you think we might need to be aware of in a medical emergency)

Medications:

Allergies:

Dietary needs:

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

Repellent Applications

Study: **Test Location:** **Date:**

	Subject Number	Sex	Limb (R or L)	Lower Limb Surface Area (square cm)	Repellent Applied (A, B)	Application Rate (mL of Repellent / square cm of skin)	mL of Repellent Applied	Time of Application	Initials of Technician

Laboratory Environmental Conditions

Study: **Location:**

Date: **Observer:**

Time	Air Temperature (degrees C)	Relative Humidity (%)	Light Intensity (lux)

Additional Comments:

Observer Signature: _____

LabEnvironConditions.xls

Tick Crossings or Repulsions at 15 Minute Intervals

Tick species: *Dermacentor variabilis*

Study:
Date:

Application Time(s):
Time of First Exposure:

Time:																				
15 Minute Interval:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Subject Number																				

Key: 0 = Repulsion, 1 = Crossing **Data Recorder Name and Signature:**_____ **Page 1 of ____**

Tick Crossings or Repulsions at 15 Minute Intervals

Tick species: *Dermacentor variabilis*

Study:
Date:

Application Time(s):
Time of First Exposure:

Time:																				
15 Minute Interval:	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
Subject Number																				

Key: 0 = Repulsion, 1 = Crossing

Data Recorder Name and Signature:_____

Page 2 of ____

Tick Crossings or Repulsions at 15 Minute Intervals

Tick species: *Dermacentor variabilis*

Study:
Date:

Application Time(s):
Time of First Exposure:

Time:																				
15 Minute Interval:	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60
Subject Number																				

Key: 0 = Repulsion, 1 = Crossing

Data Recorder Name and Signature:_____

Tick Crossings or Repulsions at 15 Minute Intervals

Tick species: *Ixodes scapularis*

Study:
Date:

Application Time(s):
Time of First Exposure:

Time:																				
15 Minute Interval:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Subject Number																				

Key: 0 = Repulsion, 1 = Crossing **Data Recorder Name and Signature:**_____ **Page 1 of ____**

Tick Crossings or Repulsions at 15 Minute Intervals

Tick species: *Ixodes scapularis*

Study:
Date:

Application Time(s):
Time of First Exposure:

Time:																				
15 Minute Interval:	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
Subject Number																				

Key: 0 = Repulsion, 1 = Crossing **Data Recorder Name and Signature:**_____ **Page 2 of ____**

Tick Crossings or Repulsions at 15 Minute Intervals

Tick species: *Ixodes scapularis*

Study:
Date:

Application Time(s):
Time of First Exposure:

Time:																				
15 Minute Interval:	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60
Subject Number																				

Key: 0 = Repulsion, 1 = Crossing **Data Recorder Name and Signature:**_____ **Page 3 of ____**

Research Subject Tracking Form

Study:

Legend: 1 =
2 =
3 =
4 =
5 =
na = Not Applicable

Subject Number																												
Subject Gender																												
MSD Sheet(s) Provided																												
Study Synopsis Provided																												
Experimental Subject Bill of Rights Completed																												
Pregnancy Test Advisory (Females)																												
Informed Consent Form Completed																												
Test Subject Contact Info Form Completed																												
Limb Measurements Completed																												
Arthropod Training Orientation Completed																												
Certified Negative Pregnancy Test																												
Repellent Efficacy Test Day 1																												
Enrolled as alternate																												

Completed By (print name, sign):

Date:

(interval number, 15 min ea)

									1				2				3				4				5				6				7				8				9				10				11				12				13				14				15	CPT (hrs)	Total crossings
Day	Date	Subject	Sex	Product	Tick	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60		
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Carroll-Loye Biological Research

711 Oak Avenue Davis, California 95616 Tel (530) 902-8267 http://www.carroll-loye.com/

CLBR Training Manual

§1.b. Handling ticks and observing their movement on the skin

A. Goals of exercise

1. Learn to move and handle ticks using a fine artist's paintbrush in preparation for participate in a tick repellent study.
2. Learn to observe ticks and measure their movement in preparation for collecting data on the effectiveness of a repellent against ticks.

B. General information

1. A technician will show you how you how to remove ticks from a plastic vial using a small paintbrush, how to avoid injuring the ticks, and how to place them on you arm and remove them, and how to dispose of them.
2. A technician will draw three lines on your forearm, each 3 cm apart. You will practice placing ticks on the arm and both watching and timing their movement in relation to those lines.
3. You will work one tick at one time. The ticks are reared in the laboratory and are free from disease.

C. Materials and equipment needed

1. Fine paintbrush
2. Marking pen
3. Approximately 6 unfed ticks
4. Labeled vials for accessing and disposing of ticks
5. Shallow pans with water
6. Timer
7. Practice data sheet and pen

D. Learning the methods

Spend about 30 minutes practicing handling ticks in the laboratory in preparation for the repellent study. Your trainer will show you how to remove ticks from vials (held in water pans in order to keep ticks from escaping). Your trainer will draw three fine lines with removable ink across your inner forearm, near the wrist, 3 cm apart from one another. From the vial labeled 'Fresh", gently touch the paintbrush tip near the front of a tick's body. It will climb onto the brush. Place the tick on the line nearest your wrist, noting the time as soon as the tick begins to walk toward your elbow. If the tick instead walks toward your hand, elevate your elbow above the hand and use the brush to gently guide the tick back toward the lines. Once it passes the first line, walking toward the elbow, note the time at that point. Observe whether the tick crosses both the second and third lines toward your elbow within three minutes of the start time. After it has crossed the third line, or after three minutes if not, use your brush to remove the tick and place it in the vial labeled 'Used'. If it crossed that line within three minutes, record 'C' on the practice data sheet; otherwise record 'R' for 'repelled'. You will practice these tasks several times in order to familiarize yourself with how to handle the ticks carefully and successfully. It is very unlikely that ticks will attempt to bite you during this training or during the actual study. However, if you see a tick stop moving and press it mouth against your skin for more than a minute, or you feel a tick begin to bite, immediately remove it with the paintbrush, and alert the trainer. You may ask your trainer for advice about any aspects of these activities at any time while you are practicing.

KBR 3023 Insect Repellent Cream

Contains Bayrepel™. Long-lasting, effective protection from mosquitoes ticks, biting flies, and fleas. Not oily, greasy or sticky. It smells great, too. Repels insects for up to 8 hours.

ACTIVE INGREDIENT: Picaridin, 1-Methylpropyl-2-(2-hydroxyethyl)-1-piperidine carboxylate	20%
INERT INGREDIENTS**	80%
TOTAL	100.0%

**Other Ingredients: Purified water, glycerin, denatured alcohol, thickener, emollient, fragrance

KEEP OUT OF REACH OF CHILDREN

WARNING

STOP – Read This Entire Label Before Use

PRECAUTIONARY STATEMENTS

WARNING. HAZARDS TO HUMANS.

Causes substantial but temporary eye injury. Do not get in eyes. Wash thoroughly with soap and water after handling, returning indoors, and before eating, drinking, chewing gum, or using tobacco. Discontinue use and consult a doctor if irritation or rash occurs.

The information below describes the first aid procedures for incidents involving KBR 3023 Insect Repellent Cream:

FIRST AID

IF IN EYES:

- Hold eye open and rinse gently with water for 15-20 minutes.
- Remove contact lenses, if present, after the first five minutes, then continue rinsing.
- Call a poison control center or doctor for treatment advice.

IF SWALLOWED:

- Call a physician or poison control center immediately for treatment advice.
- Have person sip a glass of water if able to swallow.
- Do not induce vomiting unless told to do so by a Poison Control Center or a doctor.
- Do not give anything to an unconscious person.

Have the product container or label with you when calling a poison control center or doctor or going for treatment. You may also contact 1-800-410-3063 for emergency medical information.

The LANXESS Pittsburgh Emergency Response Telephone Number is 800-410-3063

PHYSICAL HAZARDS

Flammable. Do not use or store near heat sources, sparks or open flame. Do not smoke while applying.

DIRECTIONS FOR USE

It is a violation of Federal law to use this product in a manner inconsistent with its labeling.

For best results, read and follow all label directions.

Follow these guidelines when applying KBR 3023 Insect Repellent:

- Apply evenly to skin in a thin layer
- Excessive amounts or more frequent reapplication should be unnecessary. Do not apply more than 2 times a day.
- Repels insects and ticks for up to eight hours.
- Reapply every 8 hours. Do not exceed two applications per day.
- Do not spray directly on face.
- Avoid contact with lips, cuts, wounds, or irritated skin.
- Do not apply to excessively sunburned skin.
- Do not apply under clothing.
- Apply sparingly around ears.

STORAGE AND DISPOSAL

STORAGE: Store in a cool, dry place out of the reach of children. Keep away from heat, sparks and open flame.
DISPOSAL: Do not reuse empty container. Discard in trash.
IF EMPTY: Do not reuse this container. Place in trash or offer for recycling if available.
IF PARTLY FILLED: Call your local solid waste agency or 1-800-526-9377 for disposal instructions. Never place unused product down any indoor or outdoor drain.

IN CASE OF EMERGENCY, CALL: CHEMTREC 800-424-9300
EPA REGISTRATION NUMBER: 39967-50
EPA ESTABLISHMENT NUMBER:

INTERNATIONAL 703-527-3887
Net Contents:
Lot No.:

LANXESS

LANXESS Corporation
111 RIDC Park West Drive • Pittsburgh, PA 15275-1112

LABEL TEXT DATE: 12/19/06

KBR 3023 All-Family Insect Repellent Spray

Long-lasting, effective protection from mosquitoes, ticks, biting flies, gnats, chiggers and fleas. Use with confidence on the whole family. And your family will want to use it, too. Not oily, greasy or sticky. It smells great, too.

ACTIVE INGREDIENT: Picaridin, 1-Methylpropyl-2-(2-hydroxyethyl)-1-piperidine carboxylate	20%
INERT INGREDIENTS	80%
TOTAL	100.0%

KEEP OUT OF REACH OF CHILDREN

CAUTION

STOP – Read This Entire Label Before Use

PRECAUTIONARY STATEMENTS

HAZARDS TO HUMANS

Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash thoroughly with soap and water after handling, returning indoors, and before eating, drinking, chewing gum, or using tobacco.

The information below describes the first aid procedures for incidents involving KBR 3023 Insect Repellent Spray:

FIRST AID

IF IN EYES:

- Hold eye open and rinse gently with water for 15-20 minutes.
- Remove contact lenses, if present, after the first five minutes, then continue rinsing.
- Call a poison control center or doctor for treatment advice.

IF SWALLOWED:

- Call a physician or poison control center immediately for treatment advice.
- Have person sip a glass of water if able to swallow.
- Do not induce vomiting unless told to do so by a Poison Control Center or a doctor.
- Do not give anything to an unconscious person.

Have the product container or label with you when calling a poison control center or doctor or going for treatment. You may also contact 1-800-410-3063 for emergency medical information.

The LANXESS Pittsburgh Emergency Response Telephone Number is 800-410-3063

IN CASE OF EMERGENCY, CALL: CHEMTREC 800-424-9300

EPA REGISTRATION NUMBER: 39967-53
EPA ESTABLISHMENT NUMBER:

PHYSICAL HAZARDS

Flammable. Do not use or store near heat sources, sparks or open flame. Do not smoke while applying.

DIRECTIONS FOR USE

It is a violation of Federal law to use this product in a manner inconsistent with its labeling.

Follow these guidelines when applying KBR 3023 Insect Repellent:

- Hold 4 to 6 inches from skin while spraying, keeping nozzle pointed away from face. Slightly moisten skin with a slow sweeping motion.
- Excessive amounts or frequent reapplication is unnecessary.
- Apply on face by first spraying small amounts in palms of hands and spreading on face and neck.
- Do not apply to the hands of small children.
- Repels insects and ticks for up to eight hours.
- Reapply every 8 hours. Do not exceed two applications per day.
- Do not spray directly on face.
- Avoid contact with lips, cuts, wounds, or irritated skin.
- Do not apply to excessively sunburned skin.
- Do not apply under clothing.
- Apply sparingly around ears.

STORAGE AND DISPOSAL

Store in a cool, dry place out of the reach of children. Keep away from heat, sparks and open flame.

IF EMPTY: Do not reuse this container. Place in trash or offer for recycling if available.

IF PARTLY FILLED: Call your local solid waste agency or 1-800-526-9377 for disposal instructions. Never place unused product down any indoor or outdoor drain.

INTERNATIONAL 703-527-3887
Net Contents:
Lot No.:

LANXESS

LANXESS Corporation
111 RIDC Park West Drive • Pittsburgh, PA 15275-1112

LABEL TEXT DATE: 12/19/06

SAFETY DATA SHEET

KBR 3023 ALL-FAM.INSECT REPELLENT CREAM

saltigo
customized competence
A company of the LANXESS Group

56154772

1. Identification of the substance/preparation and of the company/undertaking

Identification of the substance or preparation

Product name : KBR 3023 ALL-FAM.INSECT REPELLENT CREAM

Use of the substance/preparation : Repellent

Company/undertaking identification

Supplier/Manufacturer : Saltigo GmbH
51369 Leverkusen, Germany
Phone: +49 214 30 65109
Fax: +49 214 30 55787
E-mail: infosds@lanxess.com

Emergency telephone number : +49 214 30 99300 (Sicherheitszentrale Chemiepark Leverkusen)

2. Composition/information on ingredients

Preparation of
sec-butyl 2-(2-hydroxyethyl)piperidine-1-carboxylate CAS No.: 119515-38-7 ELINCS No.: 423-210-8

Substance/preparation : Preparation

Ingredient name	CAS number	%	EC Number	Classification
Perfume floral 12889G		0.5		N; R51/53

*** Occupational Exposure Limit(s), if available, are listed in Section 8**

3. Hazards identification

The preparation is classified as dangerous according to Directive 1999/45/EC and its amendments.

Physical/chemical hazards : Flammable.

See section 11 for more detailed information on health effects and symptoms.

4. First aid measures

First aid measures

Inhalation : If inhaled, remove to fresh air. If breathing is difficult, give oxygen. If not breathing, give artificial respiration. Obtain medical attention.

Ingestion : Wash out mouth with water. If affected person is conscious, give a copious amount of water to drink. Seek medical attention.

Skin Contact : Wash skin thoroughly with soap and water or use recognised skin cleanser.

Eye contact : In case of contact with eyes, rinse immediately with a copious amount of water. Seek medical attention.

See section 11 for more detailed information on health effects and symptoms.

5. Fire-fighting measures

Extinguishing media : In case of fire, use water spray (fog), foam, dry chemical or CO_2 extinguisher or spray.

Special exposure hazards : Flammable liquid and vapour. Vapour may cause flash fire. Vapours may accumulate in low or confined areas, travel a considerable distance to a source of ignition and flash back. Runoff to sewer may create fire or explosion hazard.

Hazardous thermal decomposition products : These products are carbon oxides (CO, CO_2), nitrogen oxides (NO, NO_2...).

Special protective equipment for fire-fighters : Fire fighters should wear appropriate protective equipment and self-contained breathing apparatus (SCBA) with a full face-piece operated in positive pressure mode.

6. Accidental release measures

Personal Precautions : Immediately contact emergency personnel. Eliminate all ignition sources. Keep unnecessary personnel away. Use suitable protective equipment (Section 8). Do not touch or walk through spilled material.

Environmental precautions : Avoid dispersal of spilled material and runoff and contact with soil, waterways, drains and sewers.

Methods for cleaning up : If emergency personnel are unavailable, contain spilled material. For small spills add absorbent (soil may be used in the absence of other suitable materials) and use a non-sparking or explosion proof means to transfer material to a sealed, appropriate container for disposal. For large spills dike spilled material or otherwise contain material to ensure runoff does not reach a waterway. Place spilled material in an appropriate container for disposal.

7. Handling and storage

Handling : Keep container closed. Use only with adequate ventilation. Keep away from heat, sparks and flame. To avoid fire or explosion, dissipate static electricity during transfer by earthing and bonding containers and equipment before transferring material. Use explosion-proof electrical (ventilating, lighting and material handling) equipment.

Storage : Store in a segregated and approved area. Keep container in a cool, well-ventilated area. Keep container tightly closed and sealed until ready for use. Avoid all possible sources of ignition (spark or flame) .

Packaging materials

Recommended : Use original container.

8. Exposure controls/personal protection

Exposure limit values : Not available.

Exposure controls

Occupational exposure controls : Provide exhaust ventilation or other engineering controls to keep the airborne concentrations of vapours below their respective occupational exposure limits. Ensure that eyewash stations and safety showers are close to the workstation location.

Respiratory protection : No special measures required.

Hand protection : No special measures required.

Eye protection : No special measures required.

Skin protection : No special measures required.

9. Physical and chemical properties

General information

Appearance

Physical state : Liquid.

Important health, safety and environmental information

Boiling point : >35°C

Flash point : Closed cup: 23 - 61°C

Vapor pressure : <1100 hPa (20°C)

Density : 0.98 - 1 kg/l

Solubility : Soluble in cold water

10. Stability and reactivity

Stability : The product is stable.

Materials to avoid : Flammable liquid and vapour. Vapour may cause flash fire. Vapours may accumulate in low or confined areas, travel a considerable distance to a source of ignition and flash back. Runoff to sewer may create fire or explosion hazard.

11. Toxicological information

Potential acute health effects

Inhalation : No known significant effects or critical hazards.

Ingestion : No known significant effects or critical hazards.

Skin Contact : No known significant effects or critical hazards.

Eye contact : No known significant effects or critical hazards.

Potential chronic health effects

Carcinogenicity : No known significant effects or critical hazards.

Mutagenicity : No known significant effects or critical hazards.

Reproductive toxicity : No known significant effects or critical hazards.

Over-exposure signs/symptoms

Inhalation : No known significant effects or critical hazards.

Ingestion : No known significant effects or critical hazards.

Skin : No known significant effects or critical hazards.

Remarks : Ames-test: negative
Micronucleus test: no clastogenic effect. (sec-butyl 2-(2-hydroxyethyl)piperidine-1-carboxylate)

12. Ecological information

Other adverse effects : No known significant effects or critical hazards.

Other adverse effects : Not available.

Special remarks on the products of biodegradation

13. Disposal considerations

Methods of disposal : Examine possibilities for re-utilisation. Product residues and uncleaned empty containers should be packaged, sealed,labelled, and disposed of or recycled according to relevant national and local regulations. Where large quantities are concerned, consult the supplier. When uncleaned empty containers are passed on, the recipient must be warnedof any possible hazard that may be caused by residues. For disposal within the EC, the appropriate code according to the European Waste List (EWL) should be used. It is

among the tasks of the polluter to assign the waste to waste codes specific to industrial sectors and processes according to the European Waste List (EWL).

Hazardous waste : The classification of the product may meet the criteria for a hazardous waste

14. Transport information

Regulation	UN number	Proper shipping name	Class	Packing group	Label	Additional Information
ADR/RID	UN1993	FLAMMABLE LIQUID, N.O.S. (CONTAINS ETHANOL)	3	III		**Hazard identification number** 30 **Limited quantity** LQ7
GGVSE	UN1993	FLAMMABLE LIQUID, N.O.S. (CONTAINS ETHANOL)	3	III		**Hazard identification number** 30 **Limited quantity** LQ7
ADNR	UN1993	FLAMMABLE LIQUID, N.O.S. (CONTAINS ETHANOL)	3	III		**Hazard identification number** 30 **Limited quantity** LQ7
IMDG	UN1993	FLAMMABLE LIQUID, N.O.S. (CONTAINS ETHANOL)	3	III		**Emergency schedules (EmS)** F-E, _S-E_
IATA	UN1993	Flammable liquid, n.o.s. (CONTAINS ETHANOL)	3	III		**Passenger Aircraft** 309: 60 L **Cargo Aircraft** 310: 220 L

Combustible
Flash point (Closed cup): 23 - 61°C
Keep separated from foodstuffs

15. Regulatory information

EU Regulations

Classification and labelling have been performed according to EU directives 67/548/EEC, 1999/45/EC, including amendments and the intended use.
- Industrial applications.

Risk Phrases : R10- Flammable.

Safety Phrases : S3- Keep in a cool place.

Other EU regulations

16. Other information

Full text of R phrases referred to in sections 2 and 3 - Europe : R10- Flammable.
R51/53- Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.

History

Date of printing : **7/19/2006**

Date of issue : **7/19/2006**

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Version : **0.02**

Prepared by : Not available.

Notice to reader

The data given here is based on current knowledge and experience. The purpose of this Safety Data Sheet is to describe the products in terms of their safety requirements. The above details do not imply any guarantee concerning composition, properties or performance.

Conforms to 91/155/EEC - 2001/58/EC - Europe

SAFETY DATA SHEET

KBR 3023 ALL-FAMILY INSECT REPELLENT SPRAY

saltigo
customized competence
A company of the LANXESS Group

56115173

1. Identification of the substance/preparation and of the company/undertaking

Identification of the substance or preparation

Product name : KBR 3023 ALL-FAMILY INSECT REPELLENT SPRAY

Use of the substance/preparation : Repellent

Company/undertaking identification

Supplier/Manufacturer : Saltigo GmbH
51369 Leverkusen, Germany
Phone: +49 214 30 65109
Fax: +49 214 30 55787
E-mail: infosds@lanxess.com

Emergency telephone number : +49 214 30 99300 (Sicherheitszentrale Chemiepark Leverkusen)

2. Composition/information on ingredients

contains
sec-butyl 2-(2-hydroxyethyl)piperidine-1-carboxylate CAS No.: 119515-38-7 ELINCS No.: 423-210-8

Substance/preparation : Preparation

Ingredient name	CAS number	%	EC Number	Classification
Perfume floral 12889G		1		N; R51/53

*** Occupational Exposure Limit(s), if available, are listed in Section 8**

3. Hazards identification

The preparation is classified as dangerous according to Directive 1999/45/EC and its amendments.

Physical/chemical hazards : Flammable.

See section 11 for more detailed information on health effects and symptoms.

4. First aid measures

First aid measures

Inhalation : If inhaled, remove to fresh air. If breathing is difficult, give oxygen. If not breathing, give artificial respiration. Obtain medical attention.

Ingestion : Wash out mouth with water. If affected person is conscious, give a copious amount of water to drink. Seek medical attention.

Skin Contact : Wash skin thoroughly with soap and water or use recognised skin cleanser.

Eye contact : In case of contact with eyes, rinse immediately with a copious amount of water. Seek medical attention.

See section 11 for more detailed information on health effects and symptoms.

5. Fire-fighting measures

Extinguishing media : In case of fire, use water spray (fog), foam, dry chemical or CO_2 extinguisher or spray.

Special exposure hazards : Flammable liquid and vapour. Vapour may cause flash fire. Vapours may accumulate in low or confined areas, travel a considerable distance to a source of ignition and flash back. Runoff to sewer may create fire or explosion hazard.

Hazardous thermal decomposition products : These products are carbon oxides (CO, CO_2), nitrogen oxides (NO, NO_2...).

Special protective equipment for fire-fighters : Fire fighters should wear appropriate protective equipment and self-contained breathing apparatus (SCBA) with a full face-piece operated in positive pressure mode.

6. Accidental release measures

Personal Precautions : Immediately contact emergency personnel. Eliminate all ignition sources. Keep unnecessary personnel away. Use suitable protective equipment (Section 8). Do not touch or walk through spilled material.

Environmental precautions : Avoid dispersal of spilled material and runoff and contact with soil, waterways, drains and sewers.

Methods for cleaning up : If emergency personnel are unavailable, contain spilled material. For small spills add absorbent (soil may be used in the absence of other suitable materials) and use a non-sparking or explosion proof means to transfer material to a sealed, appropriate container for disposal. For large spills dike spilled material or otherwise contain material to ensure runoff does not reach a waterway. Place spilled material in an appropriate container for disposal.

7. Handling and storage

Handling : Keep container closed. Use only with adequate ventilation. Keep away from heat, sparks and flame. To avoid fire or explosion, dissipate static electricity during transfer by earthing and bonding containers and equipment before transferring material. Use explosion-proof electrical (ventilating, lighting and material handling) equipment.

Storage : Store in a segregated and approved area. Keep container in a cool, well-ventilated area. Keep container tightly closed and sealed until ready for use. Avoid all possible sources of ignition (spark or flame) .

Packaging materials

Recommended : Use original container.

8. Exposure controls/personal protection

Exposure limit values : Not available.

Exposure controls

Occupational exposure controls : Provide exhaust ventilation or other engineering controls to keep the airborne concentrations of vapours below their respective occupational exposure limits. Ensure that eyewash stations and safety showers are close to the workstation location.

Respiratory protection : Use a properly fitted, air-purifying or air-fed respirator complying with an approved standard if a risk assessment indicates this is necessary.Respirator selection must be based on known or anticipated exposure levels, the hazards of the product and the safe working limits of the selected respirator.

Hand protection : Chemical-resistant, impervious gloves or gauntlets complying with an approved standard should be worn at all times when handling chemical products if a risk assessment indicates this is necessary.

Eye protection : Safety eyewear complying with an approved standard should be used when a risk assessment indicates this is necessary to avoid exposure to liquid splashes, mists or dusts.

Skin protection : Personal protective equipment for the body should be selected based on the task being performed and the risks involved and should be approved by a specialist before handling this product.

9. Physical and chemical properties

General information

Appearance

Physical state : Liquid.

Important health, safety and environmental information

Boiling point : >35°C

Flash point : Closed cup: 26°C

Density : 0.96 kg/l

Solubility : Easily soluble in cold water

10. Stability and reactivity

Stability : The product is stable.

Materials to avoid : Flammable liquid and vapour. Vapour may cause flash fire. Vapours may accumulate in low or confined areas, travel a considerable distance to a source of ignition and flash back. Runoff to sewer may create fire or explosion hazard.

11. Toxicological information

Potential acute health effects

Inhalation : No known significant effects or critical hazards.

Ingestion : No known significant effects or critical hazards.

Skin Contact : No known significant effects or critical hazards.

Eye contact : No known significant effects or critical hazards.

Acute toxicity

Product/ingredient name	Test	Result	Route	Species

Potential chronic health effects

Carcinogenicity : No known significant effects or critical hazards.

Mutagenicity : No known significant effects or critical hazards.

Reproductive toxicity : No known significant effects or critical hazards.

Over-exposure signs/symptoms

Inhalation : No known significant effects or critical hazards.

Ingestion : No known significant effects or critical hazards.

Skin : No known significant effects or critical hazards.

Remarks :

12. Ecological information

Other adverse effects : No known significant effects or critical hazards.

Other adverse effects : Not available.

Special remarks on the products of biodegradation

13. Disposal considerations

Methods of disposal : Examine possibilities for re-utilisation. Product residues and uncleaned empty containers should be packaged, sealed,labelled, and disposed of or recycled according to relevant national and local regulations. Where large quantities are concerned, consult the supplier. When uncleaned empty containers are passed on, the recipient must be warnedof any possible hazard that may be caused by residues. For disposal within the EC, the appropriate code according to the European Waste List (EWL) should be used. It is among the tasks of the polluter to assign the waste to waste codes specific to industrial sectors and processes according to the European Waste List (EWL).

Hazardous waste : The classification of the product may meet the criteria for a hazardous waste

14. Transport information

Regulation	UN number	Proper shipping name	Class	Packing group	Label	Additional Information
ADR/RID	UN1993	FLAMMABLE LIQUID, N.O.S. (CONTAINS ETHANOL)	3	III		**Hazard identification number** 30 **Limited quantity** LQ7
GGVSE	UN1993	FLAMMABLE LIQUID, N.O.S. (CONTAINS ETHANOL)	3	III		**Hazard identification number** 30 **Limited quantity** LQ7
ADNR	UN1993	FLAMMABLE LIQUID, N.O.S. (CONTAINS ETHANOL)	3	III		**Hazard identification number** 30 **Limited quantity** LQ7
IMDG	UN1993	FLAMMABLE LIQUID, N.O.S. (CONTAINS ETHANOL)	3	III		**Emergency schedules (EmS)** F-E, _S-E_
IATA	UN1993	Flammable liquid, n.o.s. (CONTAINS ETHANOL)	3	III		**Passenger Aircraft** 309: 60 L **Cargo Aircraft** 310: 220 L

Combustible
Flash point (Closed cup): 26°C
Keep separated from
foodstuffs

15. Regulatory information

EU Regulations

Classification and labelling have been performed according to EU directives 67/548/EEC, 1999/45/EC, including amendments and the intended use.
- Industrial applications.

Risk Phrases : R10- Flammable.

Safety Phrases : S3- Keep in a cool place.
S60- This material and its container must be disposed of as hazardous waste.

Other EU regulations

16. Other information

Full text of R phrases referred to in sections 2 and 3 - Europe : R10- Flammable.
R51/53- Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.

History

Date of printing : **8/29/2006**

Date of issue : **8/29/2006**

Date of previous issue : **No Previous Validation**

Version : **2**

Prepared by : Not available.

Notice to reader

The data given here is based on current knowledge and experience. The purpose of this Safety Data Sheet is to describe the products in terms of their safety requirements. The above details do not imply any guarantee concerning composition, properties or performance.

TOXICOLOGY PROFILE OF KBR 3023 (page 1 of 2)

The toxicological profile of KBR 3023 is well characterized. All toxicology data were developed using the dermal route of exposure, the most relevant route based on the use pattern of the product (insect repellent for dermal application). The rationale of product development using the dermal route of exposure was considered at the suggestion of the USEPA and in agreement with USEPA and Bayer/Miles. All study protocols, scientific issues, methodology for dermal dosing for extended periods of time and rationale for dose selection were discussed with the EPA. Agreements regarding use of dermal route of exposure were also made with BGA (German authorities) and Health & Welfare Canada. A complete toxicology package required for the registration of an insecticide including acute and subchronic neurotoxicity and metabolism studies was conducted. Additionally, 14-day, 5-week and 14-week dietary feeding studies were conducted to assess any hazard associated with hand-to-mouth transfer from dermal use of KBR 3023. The highest dermal dose for long-term studies was 200mg/kg/day. Dermal absorption studies were conducted both in rats and human volunteers to assess the human risk on the absorbed dose analysis associated with the consumer use of the product.

KBR 3023 and its formulated products have low acute toxicity by oral, dermal or inhalation routes of exposure. They were not irritating to the skin nor sensitizers in the animal studies. A slight to moderate ocular irritation was observed in the animal studies.

KBR 3023 has no demonstrable neurological or developmental toxicity by dermal route of exposure. KBR 3023 shows no evidence of genotoxicity. Subchronic dermal dosing at 500 mg/kg/day produced no clinical pathology and only slight histopathology changes in the liver, and all changes were reversible after four weeks. Chronic dermal dosing in mice, rat and dogs produced no evidence of adverse toxicity changes and it was not oncogenic in mice or rats. In the oral toxicity studies (14-day, 5-weeks and 14-weeks), only kidney effects were seen in the male rats and were attributed to α_{2u} globulin accumulation. The toxicology profile by oral route of exposure did not reveal any new targets compared to the dermal route. Cumulative effects were not evident in dermal or oral studies. The systemic NOAEL in the subchronic studies by oral route were similar (308mg/kg/day for oral/200mg/kg/day- the highest dose tested).

TOXICOLOGY PROFILE OF KBR 3023 (page 2 of 2)

The safety of KBR 3023 was further established by dermal absorption studies conducted in rats and in human volunteers. The dermal absorption study in human volunteers showed that KBR 3023 is poorly absorbed through the human skin. Only 1.66% of the material (AI) was absorbed compared to 19 – 60% for the rat. A conservative dermal penetration factor of 11.5 was used by the EPA for risk assessment. The excretion half-life in humans was 8.2 hours compared to 23.3 hours in the rat. The qualitative pattern of excretion is similar in humans and rats (primary urinary excretion) with similar metabolites. KBR 3023 has good skin feel and is odorless. No significant complaints have been reported over years of use.

In summary:

KBR 3023 has complete toxicology data supported by State-of-the–Art testing
KBR 3023 showed no foreseeable public health risks, including in children and is alternative to DEET
It has no end points of concern
Low acute toxicity
No irritant or sensitizing potential
No specific effects in rats or dogs in short-term and long-term studies
NOAEL = 200 mg/kg (dermal); NOAEL = 308 mg/kg (oral)
Not mutagenic
Not tumorigenic
No effects on reproduction
No neurotoxicity
No photo-sensitisation or irritation
It is poorly absorbed through the human skin
Does not bio-accumulate and is rapidly excreted

CITI Collaborative Institutional Training Initiative

Human Research Curriculum Completion Report
Printed on Thursday, October 30, 2008

Learner: Scott Carroll (username: scottpcarroll)
Institution: University of California, Davis
Contact Information 711 Oak Avenue
Davis, CA 95616 United States
Department: Entomology
Phone: 530 297 6080
Email: spcarroll@ucdavis.edu

Group 1.: This course is suitable for **Students, Investigtors and staff** conducting BIOMEDICAL RESEARCH with human subjects. The VA module must be completed if you plan to work with subjects at a VA facillity.

Stage 2. Refresher 2 Course Passed on 04/10/08 (Ref # 1120376)

Required Modules	Date Completed
History and Ethical Principles.	07/05/07
Regulations and Process, Part 1	10/24/07
Regulations and Process, Part 2	10/24/07
Informed Consent.	10/24/07
Social & Behavioral Research (SBR)	10/24/07
Genetics Research, Part 1	10/24/07
Genetics Research, Part 2	10/24/07
Records-Based Research, Part 1	04/08/08
Records-Based Research, Part 2	04/08/08
Records-Based Research, Part 3	04/08/08
Research with Protected Populations - Vulnerable Subjects: A Definition.	04/09/08
Vulnerable Subjects - Prisoners, Part 1	04/09/08
Vulnerable Subjects - Prisoners, Part 2	04/09/08
Studies With Minors, Part 1	04/09/08
Studies With Minors, Part 2	04/09/08
Studies With Minors, Part 3	04/09/08
Studies with Pregnant Women and Fetuses, Part 1	04/09/08
Studies with Pregnant Women and Fetuses, Part 2	04/09/08
Group Harms: Research with Culturally or Medically Vulnerable Groups.	04/09/08
FDA Regulated Research, Part 1	04/09/08
FDA Regulated Research, Part 2	04/10/08
Human Subjects Protections at the VA, Part 1	04/10/08
Human Subjects Protections at the VA, Part 2	04/10/08
HIPAA and Human Subjects Research.	04/10/08
Conflicts of Interest in Research Involving Human Subjects.	04/10/08
How to Complete the CITI Refresher Course and Receive a Completion Report	04/10/08

For this Completion Report to be valid, the learner listed above must be affiliated with a CITI participating institution. Falsified information and unauthorized use of the CITI course site is unethical, and may be considered scientific misconduct by your institution.

Paul Braunschweiger Ph.D.
Professor, University of Miami
Director Office of Research Education
CITI Course Coordinator

Return

Certificate of Completion

The National Institutes of Health (NIH) Office of Extramural Research certifies that **William Johnson** successfully completed the NIH Web-based training course "Protecting Human Research Participants".

Date of completion: 10/03/2008

Certification Number: 110234

Certificate of Completion

The National Institutes of Health (NIH) Office of Extramural Research certifies that **Shawn King** successfully completed the NIH Web-based training course "Protecting Human Research Participants".

Date of completion: 10/21/2008

Certification Number: 121628

Subject: RE: Tick shipment date; pathogen question
Date: Fri, 29 Feb 2008 10:29:40 -0500
Thread-Topic: Tick shipment date; pathogen question
From: "Levin, Michael L. (CDC/CCID/NCZVED)"
To: "Scott P Carroll" <spcarroll@ucdavis.edu>

Scott,
We always send ticks by Priority Overnight service for delivery in the morning of the next business day. We will try and send ticks on March 10-11 and will provide you with a Tracking Number.

All our uninfected colonies are "routinely" screened for the presence of the following human pathogens:

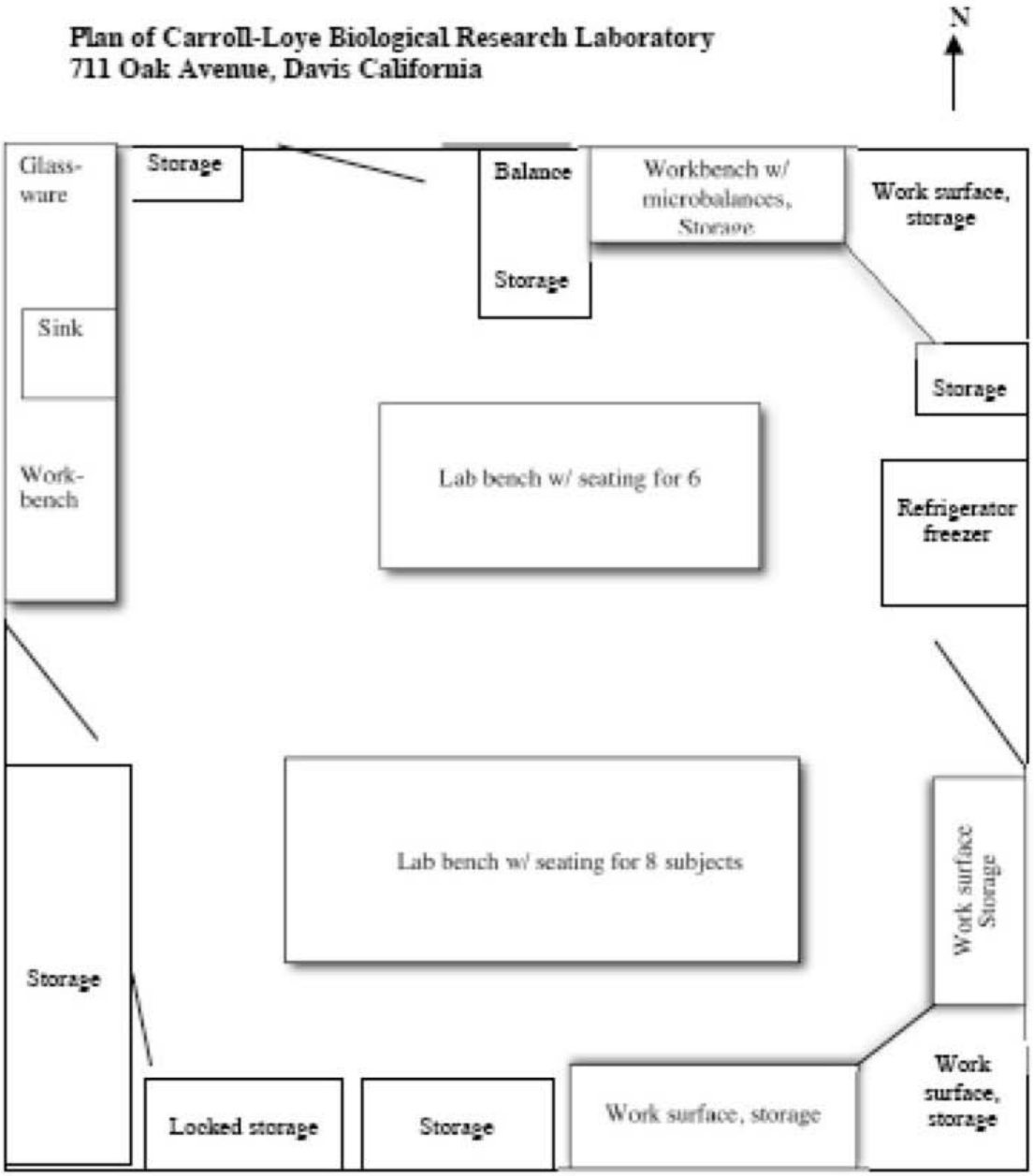
Borrelia burgdorferi
Borrelia lonestari
Anaplasma phagocytophilum
Ehrlichia chaffeensis
Ehrlichia ewingii
Rickettsia conorii
Rickettsia amblyommii
Rickettsia rickettsii

"Routinely" means:
1) Females that have laid eggs are tested by PCR for the presence of bacterial DNA in every generation – 1/generation;
2) Rabbits used for feeding of each life-stage in every tick colony, in every generation are tested for the presence of antibodies to the above-listed pathogens – 3/generation.

Let me know if I can be of more help.
Thank you
Michael L. Levin, Ph.D.

_____
Medical Entomology Laboratory
Rickettsial Zoonoses Branch
Centers for Disease Control and Prevention
1600 Clifton Road, MS G-13, Atlanta, GA 30333
Phone: (404) 639-3639
Cell: (404) 542-6608
Fax: (404) 639-4436
E-mail: MLevin@cdc.gov

Appendix 8. Physical Plan of Carroll-Loye Biological Research Laboratory



LNX-003 IRB <-> CLBR CORRESPONDENCE

IIRB, INC Meeting Minutes from Board Meeting in which Protocol LNX-003 and its Consent Documents were approved and information regarding HRPP Plan Document and Membership Roster 4 August 2009

11:57 AM Cover Email from IIRB, INC. 147
Enclosure:
Meeting Minutes 148-149

9:55 PM CLBR Inquiry to IIRB, INC. regarding most current version of HRPP Plan 150

IIRB, INC. provides latest versions of its Membership Roster and HRPP Plan documents electronically as well as Approval of August 3rd Administrative letter 5 August 2009

6:15 AM Documents emailed with cover letter 150
Enclosures:
Membership Roster *(ed. Note: Submitted as separate file)*
HRPP Plan *(ed. Note: Submitted as separate file)*

7:14 AM IIRB, INC. email to ask if files received 151

7:31 AM IIRB, INC. emails approval from review of August 3rd Administrative letter 151
Enclosures:
August 4th memo approving August 3rd Administrative Letter 152

7:58 AM CLBR email to IIRB, INC confirming receipt of Roster, HRPP Plan, and Memo of August 3rd Administrative Letter approval. 153

from	**Shawn King** <sbkingster@gmail.com>
to	Robert Roogow <rroogow@iirb.com>, Yesenia Crespo <ycrespo@iirb.com>
cc	Scott P Carroll <spcarroll@ucdavis.edu>
date	Mon, Jul 27, 2009 at 7:30 AM
subject	Initial Submission Protocol LNX-003
mailed-by	gmail.com

Hi Robert and Yesenia,

Please find enclosed for review the following documents for Carroll-Loye Study LNX-003:

Protocol
ICF (tick repellency study, so there is only a single ICF for all subjects)
ESBOR
Site Questionnaire
Study Set-up Form
Append. 2 to 6 (MSDS, toxicology, sample labels, sample data forms, subject training, staff certifications) *Ed. Note: pages 39-67 of this submission.*
Append. 13 (disease-free documentation for the tick population) *Ed. Note: page 68 of this submission.*

This study is very similar in content to our previously approved tick study SPC-002, completed in 2008, but follows our current protocol format, and has been updated to include all advancements, as applicable, derived from reviews of our more recent protocols. The Test Materials are equivalent to those in previously reviewed and approved studies LNX-001 and LNX-002, with the same MSDS, toxicology, and sample label documents.

The Protocol, ICF, and ESBOR documents are all provided as MS Word files; the ICF and ESBOR with track changes showing. In addition, the Protocol includes both page numbers and line numbers. Reviewers for both state and federal EPA find the addition of line numbers to our protocols as submitted for IRB oversight to be helpful to their review process.

The Study Monitor, Dr. G.K. Sangha, has approved the protocol, but we will also be including an approval signature from the regulatory affairs branch of the sponsor. We are expecting the scanned signature page with the third signature to be provided some time today, Monday 27 July 2009, and will forward it as soon as possible. The enclosed Protocol includes a placeholder signature page with the approval by

both the Study Director and the Study Monitor.

Please consider this submission for IIRB, Inc. full review on Tuesday 28 July 2009. We are hoping to submit to US EPA next week. As is usual we will need to provide the EPA with current versions of IIRB, Inc. Membership Roster and Policy and Procedure documents, as well as the Meeting Minutes from the meeting in which the protocol is reviewed and approved.

I can be reached by cell phone at the number below to provide immediate assistance any time today.

Thanks very much,

Best, Shawn King
--
Director of Operations
Carroll-Loye Biological Research

EFFICACY TEST PROTOCOL LNX-003

EFFICACY TEST OF KBR 3023 (PICARIDIN; ICARIDIN) - BASED PERSONAL INSECT REPELLENTS (20% CREAM AND 20% SPRAY) WITH TICKS UNDER LABORATORY CONDITIONS

Original Date:	27 July 2009
Initial IRB Approval:	Pending
Federal EPA/HSRB Review:	Pending
California EPA Review:	Pending
Ammendments:	Pending
Final IRB Approval:	Pending
Standards Applied	U. S. EPA Good Laboratory Practice Regulations (40 CFR 160); 40 CFR 26 subparts K, L and M; FIFRA § 12(a)(2)(P); California State EPA Department of Pesticide Regulation study monitoring (California Code of Regulations Title 3, Section 6710).

SYNOPSIS

This tick repellent study was commissioned by the sponsor to provide efficacy data for purposes of US/EPA registration. The test materials, based on the active ingredient Picaridin, consist of KBR 3023 All-family Insect Repellent Cream (20% Cream) and KBR 3023 All-Family Insect Repellent Spray (20% Pump Spray).

KBR 3023 (Icaridin; Picaridin) is a new generation of synthetic repellent developed as an alternative to DEET. It was developed by molecular modeling

techniques. From more than 800 substances, KBR 3023 showed the best performance regarding efficacy against a variety of arthropods (Boeckh, et al., 1996) and had the most desired attributes regarding safety, low skin penetration, and compatibility with skin, and plastic materials. It was developed by Bayer and is now owned by Saltigo GmbH (Lanxess Group) and in the USA it is handled by Lanxess Corporation (previously a Division of Bayer Corporation).

Icaridin (US EPA Registration Name Picaridin), the current common name, was developed under the Code Name KBR 3023 and the registered trade name Saltidin™ (formerly Bayrepel™) and was sold under the Brand name Autan. The chemical name for Icaridin is 1-PIPERIDINECARBOXYLIC ACID, 2-(HYDROXY-ETHYL), 1- METHYLPROPYLESTER. However, the INCI (International Nomenclature of Cosmetic Ingredients) name was given as HYDROXY METHYL ISOBUTYL PIPERIDINE CARB. The product was submitted to US EPA under the common name Picaridin. However, the common name, Picaridin, was rejected by ISO (International Organization for Standards) as it was not considered a pesticide. The common name Picaridin was also rejected by WHO/INN (World Health Organization/International Non-proprietary Name) but the common name, Icaridin, was accepted by WHO/INN

The study pursuant to this insect repellent efficacy protocol is intended to provide data under the Data-Call-In requirements (EPA Reg. No. 3126-LRN0) of United States Environmental Protection Agency Guideline OPPTS 810.3700.

Investigator (Study Director):

Dr. Scott P. Carroll
Carroll-Loye Biological Research
711 Oak Avenue
Davis, CA 95616
530-902-8267
530-297-6081 (Facsimile)
spcarroll@ucdavis.edu
http://www.carroll-loye.com/

CV on file with Carroll-Loye Biological Research

Sponsor:

Stanley C. Oslosky, Head of Regulatory Affairs
LANXESS Corporation
111 RIDC Park West Drive
Pittsburgh, PA 15275-1112

Study Monitor:

G. K. Sangha, Ph. D.
Toxicology and Regulatory Affairs Consultant
GKS International, Inc.
11411 Porter Ranch Drive #105
Northridge, CA 91326
913-638-3968

IRB:

Independent Investigational Review Board, INC.
6738 West Sunrise Blvd. Suite 102
Plantation Florida 33313
954-327-0778

Quality Assurance Unit:

Dr. William Donahue
Sierra Research Laboratories
5100 Parker Road
Modesto, CA 95357
209-521-6380

CV on file with Carroll-Loye Biological Research

TABLE OF CONTENTS

1 Justification for Research

1.1 Objective of Research and Endpoints:

The objective is to determine the duration and efficacy of the Test Material(s), when applied at a typical consumer dose, in repelling the following tick species:

Deer tick - *Ixodes scapularis*
American dog tick - *Dermacentor variabilis*

Ticks are certified disease-free laboratory-reared descendents of field caught adults. Methods employed for disease exclusion are described in Appendix 13. Ticks are reared at approximately 25°C under conditions of high humidity and long day length. Laboratory nymphs are active in questing and feeding between approximately 2 weeks and one year post-eclosion (molt). Ticks will typically be between 6 and 12 weeks post-eclosion for testing.

Individual subject dosage will be determined using the standard application rates from the dosimetry completed for related Carroll-Loye Biological Research (CLBR) studies with the Test Material(s).

Efficacy and duration will be measured as Complete Protection Time, or CPT, defined herein as the time between application of test material and the First Confirmed Crossing of an actively foraging tick from the untreated skin surface of a subject's hand 3 cm or more into the treated forearm skin area. A 'First Confirmed Crossing' (FCC) is that which is followed by another within 30 minutes.

The endpoint will be the time of failure expressed as the time of the first confirmed FCC for each subject.

The resulting data set will be suitable for submission to US/EPA to comply with the conditions of the registration.

1.2 Importance of the Research

Insect repellents are commonly used in the United State to reduce both nuisance biting and disease risk. Traditional DEET-based repellents are highly effective, but are cosmetically inferior and relatively more likely to produce mild to serious side

effects. Picaridin-based repellents are cosmetically superior and have a better safety profile. They have been marketed around the world for a decade, but only recently in the US, where they were introduced in 2005. The US Centers for Disease Control (CDC) has acknowledged the existence of substantial consumer interest in new and effective insect repellent products, including the choice of a variety of formulations, delivery systems, and concentrations of active ingredient. Of the three DEET-alternatives currently considered by CDC to have public health value, Picaridin probably has the highest broad-spectrum efficacy. However, few Picaridin products are currently available to US consumers. US EPA has requested new, US-based efficacy data as condition of registration for the test products. The purpose of this study is to provide those efficacy data. The information will also be used in product labeling.

Human subjects are required because they represent the target system for the test material, and sufficiently reliable models for repellency testing have not been developed. Repellent efficacy can only be measured in the presence of biting arthropods. Prevention of tick bites and the reduction of the risks of contracting tick-borne diseases are of substantial interest to U.S. consumers and public health professionals. Thus, there is substantial merit in its further study and the development of new repellent products toward unconditional registration by the U.S. EPA.

1.3 Balance of Risks and Benefits:

The study-associated risks are of five types: exposure to the test materials themselves, exposure to biting arthropods, possible exposure to vectors of arthropod-borne diseases, physical stress from test conditions, and psychological stress associated with a breach in confidentiality concerning pregnancy test results. As described below, subject health and safety are unlikely to be impacted by any study-associated risks during or after the study. Subject health and safety are also safeguarded by medical monitoring, assistance, and management.

1.3.1 Risks from Exposure to Test Material(s)

The repellent active ingredient has a low acute and chronic risk profile (§2), established both through experimentation and through a history of consumer use. 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 (§2).

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.

Subjects with known allergic reactions to insect repellents and common cosmetics are excluded from participating (§3.3.2). Risks associated with inhalation and ingestion would only ensue from serious mishandling by subjects, a scenario that the study methods preclude.

1.3.2 Risks from Exposure to Biting Arthropods

The risk of skin reactions to a bite is reduced by excluding candidate subjects who are aware of having a history of such reaction (§3.3.2). In addition, subjects will be trained to quickly remove any tick that attempts to bite them, before penetration or injection of saliva. Stopping Rules (§4.7.6) and Medical Management practices (§1.3.6) specify removing any treated limb from the study when the repellent begins failing or the subject shows signs of reacting to a bite or to contact with ticks. Subjects will be exposing small areas of treated and untreated skin for a maximum of 24 minutes per hour. Subjects will be teamed with others in a group for mutual observation and experienced technical personnel will be present at all times for assistance.

Within 30 days before repellent efficacy testing, subjects will be trained by technical personnel in handling ticks in the laboratory (Appendix 3). Subjects will learn how to manipulate ticks with fine paintbrushes, place them on their own forearms, observe and quantify tick movement on their arms, and dispose of used ticks. This training will be documented. This 'hands-on' experience will assist subjects in collecting data accurately and handling ticks safely during the repellent efficacy trial. This procedure also serves to verify the subject's attractiveness to ticks in the study.

1.3.3 Risks from Exposure to Disease Vectors

Our laboratory-reared tick populations are certified disease free (Appendix 13). There is no risk of tick-vectored diseases for subjects in our laboratory tests.

1.3.4 Physical Stress in the Test Environment

Physical stresses on subjects are minimized by careful preparation and provisioning. Lab testing environments are temperature and humidity controlled to remain well within human comfort zones. The testing area is maintained free of tripping hazards, and an adjacent rest area is stocked with food, water, and beverages. Seating is provided for all subjects. Private bathroom facilities are also provided on site.

1.3.5 Maintaining Privacy of Pregnancy Test Results

Section 3.3.2 lists the exclusion criterion detailing pregnancy test procedures. Results of a subject's test are only observed by one female CLBR staff technician and never recorded to minimize stress on a female subject testing positive, and minimize the possibility that other staff or subjects may become aware of the results of that test.

1.3.6 Medical Monitoring, Assistance, and Management

Subjects are clearly and repeatedly informed that they may remove themselves for any reason from the study at any time, without penalty to their compensation. 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 7 days of the conclusion of the test day.

On the test day, staff will immediately communicate all subject concerns about health, safety, or comfort to the Study Director for assessment. The Study Director will also assess skin condition of affected subjects should any bites inadvertently occur during efficacy testing, or any subject reports any discomfort in treated areas. Subjects are instructed to inform the Study Director (i.e., the 'Principal Investigator'), or any other staff member if at any time during the study a subject suffers a skin reaction, such as redness, edema, itching or pain, or feels ill. Such subjects will be immediately withdrawn from testing and tick exposure, and medical management will be implemented. When a subject completes the study or is removed for any reason, treated skin areas will be gently washed with clean water and mild soap, rinsed with a 35% ethanol in water solution, then gently dried with a towel to remove test materials.

When medical management is implemented, the Study Director will contact the On-Call physician for the study and comply with the physician's instructions. On the day of testing, a physician who has read the protocol and discussed the research with the Study Director will be on call. Contact information for the nearest medical facilities and maps from the test site to the facilities will be prepared and on file before the day of testing. In unlikely event of a Type 1 allergic reaction (anaphylaxis), we will contact 9-1-1 by cellular or ground-line telephone and cooperate as instructed with emergency personnel. Epi-Pens will be on-site. At least one qualified researcher will remain with the other test subjects if other researchers depart with an injured or ill subject. We will be prepared to instruct emergency personnel on 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.

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.

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

1.3.7 Summary of Risks and Benefits

The combination of technical precautions and natural factors means that the chances that any subject will contract disease, suffer an injury, or suffer a severe reaction from a tick bite are extremely small.

Against these slight risks are balanced substantial and reasonably likely benefits. The principle beneficiary will likely be the Sponsor, for whom new data and new labeling will meet current US EPA registration standards. Because EPA registration requires efficacy data, a test such as that proposed here is the only path toward further product development, greater availability, and increased consumer acceptance of new repellent formulations in the United States. For the general public, tick-borne disease is of growing significance in the United States and around the world where U.S. citizens are active. Moreover, discomfort associated with nuisance biting restricts many work and pleasure activities

2 Test Material(s): Description and Control

The following table summarizes all information about the test material(s) relevant to this study.

Test Materials as referred to in this Protocol:

	Cream 20%	Spray 20%
Test Material name (Picaridin conc.)	KBR 3032 All-Family Insect Repellent Cream (20%)	KBR 3023 All-Family Insect Repellent Spray (20%)
Manufacturer	LANXESS Corporation	LANXESS Corporation
Manufacturing Standards Applied	Good Manufacturing Practice standards, with records available to EPA.	Good Manufacturing Practice standards, with records available to EPA.
Transport	Commercial Courier, express, insulated container	Commercial Courier, express, insulated container
Chain of Custody	Documented	Documented
Specific gravity	0.98	0.96
Delivery system	Lotion	Pump Spray
Active ingredient(s) (%)	Picaridin 20%	Picaridin 20%
Inert ingredients	Proprietary, available to US EPA	Proprietary, available to US EPA
Stability	Stable	Stable
Storage conditions specified	Room temperature, max 30° C (86° F)	Room temperature, max 30° C (86° F)
Storage conditions applied	Locking, closed cabinet at room temperature (19-24°C) protected from light and moisture sources	Locking, closed cabinet at room temperature (19-24°C) protected from light and moisture sources
Description of cosmetic properties	White cream	Clear solution
NOAELs for Picaridin	NOAEL = 200 mg/kg (dermal); 308 mg/kg (oral)	NOAEL = 200 mg/kg (dermal); 308 mg/kg (oral)
Irritation and sensitization class	(Picaridin) No irritant or sensitizing potential	(Picaridin) No irritant or sensitizing potential
Hazard label requirements	Substantial but temporary eye injury. Do not get in eyes. Wash thoroughly with soap & water after handling, returning indoors, and before eating, drinking, chewing gum, or using tobacco. Discontinue use and consult a doctor if irritation or rash occurs; Flammable.	Moderate eye irritation, avoid contact with eyes or clothing, wash thoroughly with soap & water after handling, returning indoors, and before eating, drinking, chewing gum, or using tobacco. Flammable.
Reference materials	Sample labels in Appendix 4, pages 52-53 MSDS and Toxicology documents in Appendix 5, pages 54-65	

The sponsor is responsible for completing all toxicological screening, compositional analysis, and stability studies for the test material(s) and providing the results to Carroll-Loye Biological Research prior to providing the test material(s) to Carroll-Loye.

3 Research Subjects: Recruitment, Screening, Consent, Privacy

3.1 Candidate Recruitment: Population, Sampling Frame, Representativeness

For reasons of practicality and control, we work with people associated the community in which our business is located (Davis, CA). Davis is a university-dominated community, and so the population demography differs somewhat from non-university communities. Compared to the Population of Concern (the US population - all potential repellent users), our sampling frame tends to under-represent blacks and over-represent Asians. It is also young, well educated, and slanted towards life science researchers and students.

Over time, we have developed a Volunteer Database of individuals who have expressed interest in participating in future repellency tests, provided contact information, and asked us to contact them. Initial recruiting is from this database, then from word-of-mouth of volunteers. The size and composition of the database varies over time as new individuals volunteer and old volunteers move out of the Davis area, but is now typically over 100 individuals, with the following average ethnic (self-identified) and gender distribution (averaged over 3 years):

Male	52%
Female	48%
Caucasian	74%
Asian	12%
Hispanic	7%
African-American	4%
Arabic	3%

In general, about three-quarters of the subjects are age 20-40, with the remainder between 40 and 55. Final composition is not determined until enrollment is completed. The relevant demographics of the participants will be reported.

Carroll (2006) 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 ectoparasite, or likely impact on a repellency trial's data set. Several studies have indicated that individuals differ in attractiveness to mosquitoes, for example, but individual attractiveness rankings shift substantially among parasite taxa. Skin-emanated volatiles influence attractiveness, as do skin temperature and absorption properties; these factors may likewise influence repellent efficacy. Studies of gender, age, race, hair color, complexion, weight, skin moisture, menses (females), hairiness, and sweat have shown only gender to have significant effects on individual attractiveness to mosquitoes. Though studies have shown that sweating increases attractiveness to at least one mosquito species, it is not clear whether individuals that sweat more than others, on average, tend to be more attractive to mosquitoes. Two studies with adequate sample sizes found females to be 25% less attractive to *Aedes* mosquitoes, while the other showed them to be significantly less well protected against *Anopheles* mosquitoes by 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 attempt to enroll similar numbers of males and female subjects.

On the other hand, it *is* clear that conditions of use strongly influence repellent performance. We intentionally test under conditions of light, temperature and humidity conducive to tick foraging behavior. Further, we expose subject individuals as uniformly as possible to the ticks, and have them handle the ticks in ways that minimally disrupt tick behavior. We also monitor subjects 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 arthropod-borne diseases (see above), though the likelihood of contracting the causal agent during a repellent test is very low.

Based on review of the scientific literature regarding individual differences in repellent performance and attractiveness to ticks, we conclude that this study's deviations from the ideal frame will not influence the representativeness of the results, or their generalizability to the greater population. Lastly, because our Volunteer Database cohort is comprised by individuals who regularly spend time in outdoor setting (and thereby may have relatively frequent encounters

with biting arthropods), this group is probably appropriate for insect repellent users in general.

3.2 Candidate Recruitment Procedures

Recruitment for the Repellency Phase begins as soon as the test dates are determined.

Potential candidates are initially contacted by phone from our Volunteer Database and queried about interest and availability. Individuals are chosen using a random number table to choose subject numbers from the database and contacted. During the phone interview, we also inform potential candidates that they are permitted to refer others to us by having them contact us. Recruitment continues until the roster of subjects and alternates is full.

3.3 Candidate Screening

3.3.1 Inclusion Criteria, all subjects

Age: 18-55 years
Sex: Male/female
Race: Any race
Completed Consent Process (§3.4) including providing Written Consent (defined as having read, initialed, dated and signed Informed Consent Form and Experimental Subject Bill of Rights)
Language: Speak and read English

3.3.2 Exclusion criteria, all subjects:

1. Known to be hypersensitive to tick bites or exhibiting hypersensitivity during test
2. Phobic of ticks
3. Known to be allergic to insect repellents or common cosmetics
4. Known to be sensitive or showing sensitivity to any of the test product ingredients after application.
5. Poor physical condition.
6. Unwilling to submit to brief query about personal condition.
7. Use of insect repellent within one day preceding the efficacy test.
8. Unwilling to refrain from use of perfumed products, alcoholic beverages or smoking after 9 PM the evening preceding the efficacy test and throughout that test.

9. Known to be pregnant or lactating. Each female volunteer of child bearing potential will self-check for pregnancy using an OTC test kit provided by a technician on the day of any study visit in which repellent will be applied or in which the subject will be exposed to ticks. Results of each such test will be immediately verified by direct inspection by a female technician experienced in making that assessment. Information regarding pregnancy test results will be kept in confidence. Only volunteers scored as nonpregnant will be allowed to participate.
10. Unable to deliver the test materials or nymphal ticks to own left and right arms.
11. Unable to see nymphal ticks on skin or otherwise effectively monitor them on skin.
12. Student or employee of the Study Director.
13. Does not regularly spend time in outdoor settings.
14. Withdraws from testing before receiving a confirmed crossing, 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.
15. Not attractive to target species.

3.4 Obtaining Subjects' Consent

All candidates are screened or re-screened for suitability for each test in a private, one-on-one conversation with the Study Director, at which time the Exclusion Criteria (§3.3.2) are exercised by asking each candidate to address them. It is explained to female candidates of child bearing potential that pregnancy will be assessed directly on the day of any study visit in which repellent will be applied.

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 that pass screening, the Study Director describes the test purpose in plain language (in English), and the procedures and comportment to be followed are described. Candidates are then asked if they would like to retire from consideration at that point. 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 from a distant site), to discourage the subject from believing that the considerable effort or expense creates an added obligation to participate.

If the candidate indicates he or she wishes to proceed, the Study Director provides a copy of this study's IRB-approved Informed Consent Form (ICF) and State of California Department of Pesticide Regulation 'Experimental Subjects' Bill of Rights' (BOR) for review (Appendix 1). The candidate is also offered their own copy of the protocol itself, and supporting documents (MSDSs, toxicology study results, compositional analysis of the Test Materials, and training documents) for review. In a private session a senior CLBR staff member certified in protecting human research participants by the National Institute of Health (NIH), will read the ICF and BOR documents out loud with the candidate, offering to take questions and answering any that arise. The amount and form of compensation is described.

Candidates 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, or work directly with or otherwise regularly encounter biting arthropods 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 following due consideration. Nonetheless, the Study Director retains the final right to refuse participation to any candidate.

When all screening procedures are complete, the candidate is asked to sign, initial, and date the ICF and BOR for this study, both of which are then cosigned by a NIH certified staff member of Carroll-Loye. The candidate, now a subject, is then asked to complete a contact and emergency medical form

3.5 Protecting Subjects' Privacy

Screening interviews are conducted in private and one-on-one. All written records containing names, contact information, medical information, and signatures are kept in a locked, fire-proof cabinet. Access to these files is restricted to Carroll-Loye staff with the Study Director's permission. All subjects are assigned a unique number to identify them on all data forms and to staff and other subjects during testing activities. Although many subjects interact socially during the tests, and may voluntarily share names or other personal information, subjects are never asked, required, or encouraged to do so. 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 at any time.

We will enroll three 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 who 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.

4 Study Design

4.1 Number of Subjects

In efficacy testing, we will use 10 subjects per treatment. Each subject is a replicate. Ten subjects are two-thirds more than the historical EPA requirement of six subjects. EPA is currently working on more precise guidance on sample size, but that remains forthcoming.

The number of subjects is chosen as a compromise among multiple factors. The goal is to meet regulatory requirements to provide an estimation of the true mean CPT, and so from a scientific standpoint an appropriate response under such circumstances is to increase size, but ethical and economic considerations demand the opposite in the present study, particularly during the efficacy-testing phase.

Importantly, under the historical guidelines, there seem to have been few problems with EPA registering repellents failing to meet their labeled performance specification. Nonetheless, there are clear risks in using a very small sample, and conspicuous among them in this study is that the probability of over-representing subjects inherently unattractive to the target species is rather large. We reduce this risk by confirming subject attractiveness to ticks before they participate in the phase of the test where efficacy data is collected. This should decrease the probability of certain sampling errors substantially.

For calculating EPA-required mean and variance data, estimating the power associated with a given sample size is constrained by three factors, namely, little knowledge of the magnitude of individual CPT values in tick studies, little information regarding the distribution of CPT values in insect repellent studies in general, and, the first consideration notwithstanding, a reasonably high chance that there will be a number of censored values. If a minority of values is censored, and particularly if the range of values is not great (as in related mosquito repellent study LNX-001, MRID 47506401), a sample size of 10 should give excellent estimates of mean, median, and variation around those values, relative to historical standards. Still, 10 is sufficiently small, from both statistical and biological perspectives, that we are confident that we are not oversampling.

EPA has expressed interest in refining how CPT data are assessed and analyzed. We judge that such improvements are best made in the context of a further formalization of how EPA makes its labeling decisions from CPT data sets. The central ideas stem from types of survival analysis. One suggestion is to use, e.g., the time to 25% failure (among subjects) as the labeled protection time (when censoring is not too frequent). Another would require the Agency to specify acceptable Type I error probabilities for estimates of minimum CPTs *exceeding* a specified value. With the latter approach, EPA would also have to judge how to label with respect to the confidence interval around such probability estimates. Like the typical estimation of means and standard deviations, the soundness of such alternative statistical judgments will hinge on the accuracy of assumptions regarding the nature of the population distribution.

Given the success of past practices in application, and our clear improvements in sample size, it is premature for us to suggest further substantial change in how the EPA assesses repellent efficacy data. The basic philosophy, and therefore methodology, of how these data are analyzed should be based on a clear and stable agency strategy regarding the information content of product labels.

4.2 Number of Controls

Each subject simultaneously serves as a treatment and control subject. Ticks are placed on the untreated arm of the subject to determine foraging avidness, then moved to the treated arm. The 'negative control' for efficacy data sets serves to insure that each tick employed in the study is attracted to the test subject before it is used in a repellency challenge. Ticks that fail to meet the questing criterion (§4.8.2.1) are not used against Test Materials. In this way the negative control serves as a pre-screening of the ticks, such that only actively questing ticks are then exposed to the treatments. Based on this manipulation of a standard control design, the crossing rate on the negative control is judged to be 100%.

4.3 Controls for Matrix Materials

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

4.4 Controls with Comparison Materials

There are no comparison materials in this study. Questions of comparison between the Test Materials and other repellents are external to the objective.

4.5 Subject Measurements

We will measure length and circumference of the forearms of subjects. Circumference will be measured at four points (upper forearm, lower forearm, and two equally spaced points in between). This data will be averaged for mean circumference, which will be multiplied by length to calculate surface area. This data will be kept on file for each subject. Subjects will be re-measured bi-annually or if, when asked, they indicate they may have gained or lost weight or muscle mass on their limbs since their measurements were last taken. This practice reduces the frequency of potentially invasive repeated measurement procedures for subjects.

4.6 Standard Dose as Determined by Dosimetry

Dosimetry data are used to determine individual dosing for efficacy testing. Dosing rates are calculated on a per square cm basis. Those rates were obtained in a dosimetry study of each test material in 2007 during our conduct of an earlier study reported as LNX-001 (MRID 47506401).

Dosing Rates, by Test Material

	arms
Cream 20%	*2.51 μl/cm^2
Spray 20%	0.97 μl/cm^2

*We are currently in the process of negotiating with EPA concerning additional dosimetry data collection for the Cream 20% product to augment the data set. Depending on the outcome of the negotiations, we may amend this protocol to include augmented data in the final dosage determination.

The dosing rate for each Test Material is the grand mean rate calculated from 10 subjects (converted from weight to volume by reference to the specific gravity of each test material).

4.7 Efficacy – Components of the test

The efficacy study will consist of one laboratory trial. In each trial, each Test Material will be tested with 10 subjects. The individual subject will be the experimental unit.

Using a mean application rate derived from dosimetry (§4.6), individual dosages will be prepared for each subject volumetrically such that for each Test Material, all subjects receive the same amount of Test Material per unit

skin area exposed. Skin surfaces of both treated and untreated limbs are first cleansed with water and a fragrance-free detergent soap, rinsed with a 35% ethanol in water solution, and then towel-dried. Test Material is dispensed from tuberculin (1 ml) syringes by technicians wearing surgical gloves who apply it to treated subjects by spreading evenly over the area to be treated using one finger in a light rubbing motion. Application of each Test Material is considered a treatment. All treated limbs are monitored to minimize abrasion with clothing or laboratory surfaces from the time of application.

All subjects will be assigned to the treated group, which will be blocked by gender. The treatments will be allocated in sequence ('A', then 'B', then 'A', etc.). Within each gender, the treatments will be allocated at random excepting minor adjustments needed to constrain the numbers treated with a particular Test Material to 10. The treatment each subject receives and the time of application for each subject will be recorded on a data capture form (Appendix 2). Multiple technicians will make the applications, and each application will take only about two minutes to complete, so that subjects receiving 'A', for example, will not be treated on average significantly earlier than those treated with 'B'.

Materials will be distributed among subjects as tabulated below.

Subject	**Cream 20%**	**Spray 20%**
1	Left arm	
2	Left arm	
3	Left arm	
4	Left arm	
5	Left arm	
6	Right arm	
7	Right arm	
8	Right arm	
9	Right arm	
10	Right arm	
11		Left arm
12		Left arm
13		Left arm
14		Left arm
15		Left arm
16		Right arm
17		Right arm
18		Right arm
19		Right arm
20		Right arm

695
696 4.7.1 Blinding of Study
697 Because the treated condition will be evident to researchers, technicians, and
698 subjects, neither staff nor subjects will be effectively blinded. However, within
699 the treated group, the three treatments will be indistinguishable to test subjects
700 and staff based on their physical properties. Accordingly, the three treatments
701 will be coded 'A' or 'B' by a technician. That technician will dispense the test
702 materials so labeled for efficacy test treatments. That technician will not be
703 involved in judging crossing events during efficacy data collection.
704
705 The treatment code key will be recorded in hardcopy by the technician and
706 maintained in a locked file drawer to which only he/she has the key. As a
707 backup, the key will also be recorded in a password protected computer file.
708 For backup access, two technicians will be charged with privately maintaining
709 the password offsite from the laboratory. Technicians will be charged not to
710 reveal the code or the specific identity of test materials at any time during
711 application or data collection, unless needed for medical or legal reasons. The
712 Study Director will retrieve the code key from the technician(s) after the
713 conclusion of data collection.
714
715 This moderate level of blinding security is deemed appropriate for a test in
716 which the performance difference between untreated and treated conditions is
717 unlikely to be ambiguous, and in which the performances of the test materials
718 are not specifically being compared.)
719
720 4.7.2 Target Arthropods
721 Species challenging the repellent in the test are listed in §1.1. We will test
722 repellency against deer tick - *Ixodes scapularis,* and American dog tick -
723 *Dermacentor variabilis*.
724
725 4.7.3 Confirming Tick Foraging Activity
726 To be included in the test on a treated limb, each tick must first meet the
727 crossing criterion on the untreated limb, following the procedure for the treated
728 limb in the same test period (§4.8.2.1).
729
730 4.7.4 Measuring Repulsion
731 The number of crossings on each subject's exposed treated area will be
732 recorded (Appendix 2) as they occur during 3-minute exposure periods
733 commencing once every 15 minutes, beginning at the onset of data collection
734 and ending when the subject receives the First Confirmed Crossing, a stopping
735 rule is invoked for the subject, or the Study Director stops the test for all

subjects. Based on repellency trials of the Test Material(s) against mosquitoes (related study LNX-001, MRID 47506401), we expect the repellents may remain effective for up to 12-14 hours possibly more.

4.7.5 Environmental Conditions – Data

Records (Appendix 2) of presence/absence and general rate/quality data for environmental conditions (temperature, relative humidity, light intensity) will be made at approximately one-hour intervals throughout the course of the laboratory trial.

4.7.6 Stop Rules

All subjects

- Consented duration reached
- Test site becomes unsafe for subjects for any reason
- Foraging pressure falls below threshold needed to challenge the Test Material(s)

Individual subjects

- Subject asks to withdraw
- Subject proves unattractive to target species
- Subject's treated limb receives Confirming Crossings for both target species
- Medical management is invoked for the subject (§1.3.6)

4.8 Sequence of efficacy test procedures

4.8.1 Within 60 days preceding Test Day

Candidate screening and subject consenting and orientation will occur.

4.8.2 1 Day prior to test

Staff prepare laboratory, arranging space in the facility to accommodate all test subjects and staff. A separate area for dispensing food and beverages is prepared and provisioned for subject access throughout the test.

4.8.3 Test Day

Subjects gather at the Carroll-Loye Biological Research laboratory to clean limbs and receive applications. 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. Subjects are also reminded of procedures for the day's test.

The following test procedures are repeated by each subject at designated time intervals until a stop rule (§4.7.6) is invoked.

4.8.3.1 Tick screening for active foraging and repellency challenge

Three 'orientation' ink dots are arrayed longitudinally on both ventral forearms of each subject, at 3 cm intervals. On the treated arm, the first dot is 3 cm distal to the treated area, the second dot marks the threshold of the treated area, and the third dot is 3 cm into the treated area. The untreated limb/limb portion has a spatially identical array of 3 lines for tick activity screening. The first dot, used for placement, insures that ticks are not placed within the treated area and so can detect a gradient of repellent density to which to orient. The second dot serves keep subjects aware of where the treated area begins and serves as a reorientation point for re-marking should either the first or the third dot become obscured.

Subgroups of approximately three subjects are led by a technician in the monitoring of time, ticks, and tick behavior. Every 15 minutes, each subject selects an unused tick and screens it for active questing behavior, repeating until an actively questing tick is identified. The subject then transfers the tick to the treated arm for a repellent challenge.

To initiate a screening or a repellent challenge, a tick is placed on the ventral arm or proximal palm, in the most hair-free portion, at the first (most distal line). Ticks are manipulated with the bristles of a fine artist's paintbrush. Ticks are placed so that they face the elbow. Ticks may be oriented to locomote toward the margin of the treated area with the gentle action of the paintbrush. Forearms should be held from approximately 30° to vertically above the lab bench surface if that increases the propensity of ticks to travel toward the body.

Active questing is verified if a tick travels past the second marker dot in motion towards the elbow on the untreated arm. On the treated arm, a crossing is scored if a tick travels at least 3 cm in a vector toward the elbow into the treated area (i.e., at least as far as the third line) within 3 minutes of beginning to move up the arm from the first line. A repulsion is scored when a tick changes its orientation away from, or parallel to, the margin of the treated area upon approach, or does not cross more than 3 cm toward the elbow within 3 minutes of entering the treated area.

4.8.3.2 Repellency data collection and tick removal

The technician will assist subjects in determining crossing versus repulsion events, and in determining whether a tick may be beginning to bite (an extremely unlikely event), and assisting in removing a tick should a bite occur (no embedding is

anticipated, so removal should be possible with the same small paintbrush). Time is monitored by referring to an electric chronometer with a highly visible display. The technician will record any crossings or repulsions as they occur. Repulsions are normally unambiguous reversals of direction. Subjects lift the tick off with the paintbrush after each assessment is complete. Any brushes that come into contact with a test material are discarded. Used ticks are immediately retired from the study by being transferred from the test arm to a container labeled "used".

4.9 Efficacy – Statistical design and analysis

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

Because all subjects use different ticks, all ticks are used only once, and neither organism interacts directly with conspecifics at the level of the skin and the repellent during data collection, we will analyze data by subject as independent, replicated values. The hypothesis that the test materials will significantly reduce the number of ticks Crossing treated versus untreated skin is not the objective of this study. The objective is to compute, for each test material, a reasonable estimate of mean and standard deviation for the duration between application and sufficient repellency breakdown such that there are two ticks crossings on a subject within a half hour period. That pattern is here assessed at a resolution of 15 minutes.

For each treated subject, we will measure (data form Appendix 2):

- Exposure delay (min) – time between application and first exposure
- Minutes to First Confirmed Crossing (FCC) or end
- Complete Protection Time (CPT) – time between application and FCC

Complete protection time (CPT) is measured as the length of time from initial application to the First Confirmed Crossing (FCC). A FCC is a Crossing followed by another Crossing within 30 minutes. For example, a Crossing at 90 minutes followed by another at 135 minutes is not confirmed, but a third Crossing at 150 minutes would confirm the one at 135 minutes, giving a CPT of 135 minutes.

CPT is measured as a single time value for each subject. Based on the requirements for such estimates in the EPA draft repellent efficacy testing guidelines (1999; OPPTS 810.3700), we will calculate mean CPT across all 10 subjects, with standard deviation and 95% confidence interval information.

Data will be normalized as possible to enhance the value of confidence interval calculations.

As described in §4.74, we anticipate that protection may span up to about 12 hours, and possibly 14 hours or more after application for some subjects. To examine the temporal pattern of failure further, we will employ Kaplan-Meier survival analyses by subject. Kaplan-Meier survival analysis accommodates some data censoring in the event that any subjects withdraw or are withdrawn before failure. In addition, we will estimate the Kaplan-Meier median, and the time until 25% failure, for each test product. In the presence of a high frequency of censoring, median (and mean) values will be underestimated.

Our chosen sample size of 10 subjects will improve precision in estimating test material 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. The resulting data set will be provide values suitable for any additional statistical characterizations of repellent performance that EPA may wish to employ in developing labeling language for the Test Materials.

5 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 technicians. 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 both the Study Director and to the Sponsor Monitor.

6 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 as well as 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.

7. LITERATURE CITED AND SELECTED REFERENCES

Bernard, Donald R., Bernier, U. R., Posey, K. H. and Xue, Rui-De (2002). Repellency of IR 3535, KBR 3023, para-menthane-3,8,-diol, and DEET to Black Salt Marsh Mosquitoes (Diptera: Culicidea) in Everglades national Park). J. Med. Entomology 39(6): 895-899

Boeckh, J.; Breer, H.; Geier, M.; Hoever, F. P.; Kruger, H. W.; Nentwig, G.; Sass, H. Acylated. 1,3-aminopropanols as repellents against bloodsucking arthropods. Pestic. Sci. 1996, 48, 359-373.

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.

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

Constantini, Carlo and Ilboudo-Sanogo, Edith (200-). WHOPES Evaluation of Insect Repellent KBR 3023 in Burkina Faso. Final report for WHO Project V2.181.276

Frances, S.P., Waterson, N.W., Beebe, N.W. and Cooper, R.D. (2004). Field Evaluation of Repellent Formulation Containing DEET and Picaridin against Mosquitoes in Northern Territory, Australia. J. Med. Entomology 41(3): 414-417

Frances, S.P., Van dung, N., Beebe, N. W. and Debboun, M. (2002). Field Evaluation of Repellent Formulations against daytime and Nighttime Biting Mosquitoes in a Tropical forest in Northern Australia. J. Med. Entomology 39(3): 541-544

Luepkes, K. H. Mosquito repellent effects of various formulations based on Bayrepel / KBR 3023 against yellow fever mosquito Aedes aegypti (2005). Unpublished Lanxess report

Yap, H. H., Jahangir, K., Chong, A.C.S., Adanan, C. R., Malik, Y. A. and Rohaizat, B. (1998). Field Efficacy of a New Repellent, KBR 3023, against Aedes albopictus (SKUSE) and Culex quinquefasciatus In a Tropical Environment. Journal of Vector Ecology 23(1): 62-68

Yap, H.H., Jahangir, K. and Zairi, J. (2000) Field Efficacy of Four insect Repellent Products against Vector Mosquitoes in a Tropical Environment. Journal of the Mosquito Control Association. 16(3): 241-244

8 Protocol Approval Signatures

Scott P. Carroll, Ph.D.
Study Director

July 26, 2009
Date

Stanley C. Oslosky
Head of Regulatory Affairs
LANXESS Corporation

Date

G. K. Sangha, Ph. D.
Study Monitor

July 26, 2009
Date

INFORMED CONSENT AUTHORIZATION TO PARTICIPATE AS A RESEARCH STUDY SUBJECT

Title of Study: **LNX-003** EFFICACY TEST OF KBR 3023 (PICARIDIN; ICARIDIN) - BASED PERSONAL INSECT REPELLENTS (20% CREAM AND 20% SPRAY) WITH TICKS UNDER LABORATORY CONDITIONS

Principal Investigator: Scott P. Carroll, Ph.D.
Carroll-Loye Biological Research
711 Oak Avenue
Davis, CA 95616
(530) 902-8267

Site of Investigation: Carroll-Loye Biological Research
711 Oak Avenue, Davis, CA 95616

Sponsor: LANXESS Corporation

Participant's Name: _____

INTRODUCTION

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 request, we will also provide you with a copy of the study Protocol, which details all the procedures of the study, and contains details about product safety. 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 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. 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 cream and pump spray formulations, works against two types of ticks. The information gained from the study will assist in developing these repellents for commercial marketing. During the study, we will test the insect repellents against ticks in a laboratory.

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APPROVED BY
Independent IRB

Signature Date

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Date: _____

The sponsor, LANXESS Corporation, 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. Using an over-the-counter (OTC) pregnancy kit supplied by a technician, you will perform a pregnancy test at the laboratory on the day of any study visit in which repellent will be applied or in which you will be exposed to biting insects. Your test results will be verified by a female technician experienced in making that assessment. 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. If you decide to withdraw from the study after taking the pregnancy test you do not need to show a positive result.

RESTRICTIONS

- You must not be a student or employee of the Principal Investigator.
- You must not be hypersensitive (allergic) to tick bites, or phobic of ticks.
- You must not be sensitive to any of the test product ingredients, or allergic to common cosmetics.
- You must regularly spend time in outdoor settings.
- You must be able to see and remove ticks that come in contact with your skin.
- 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. To meet this restriction, you may need to purchase fragrance-free cosmetics prior to the test days. If you do, you will be reimbursed for your expenses.
- 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 repellency testing.

NUMBER OF SUBECTS PARTICIPATING

Up to about 23 subjects will be enrolled. 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

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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	Visit 2
1. Orientation visit	X	
2. Field study visit		X
Total time	2-2.5 hours	8-16 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

Within 30 days before the second visit (in which we will test the repellents against ticks), 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 will also be shown how handle ticks on your skin with a small artist's paintbrush. This training and practice will take about ½ hour.

The total time for Visit 1 activities will be about 2-2.5 hours.

Visit 2 for the Tick Repellent Test

The study will also require a second visit to the same laboratory. This second visit will most likely require approximately 12 hours of your time. However, it may require as few as about 4 hours or many as about 16 hours, depending on how long the repellents remain effective. Bathrooms are available, and meals, drinks and snacks will be provided.

STUDY PROCEDURES

Visit 1

At the laboratory, a researcher will measure the length and circumference of your forearm. If you have participated in a Carroll-Loye Biological Research study within the last two years, and were measured for that study, we will use your on-file limb measurements unless, when asked, you indicate that you think you have gained or lost weight or muscle mass on your limbs since the previous measurements were taken.

You will also be given a verbal orientation to the activities of the test day, with an opportunity to ask the researcher questions or share your concerns about any aspect of the research activities.

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At the laboratory, you will spend about 30 minutes practicing handling ticks in the laboratory in preparation for the repellent study. A technician will show you how to catch the ticks, place them on your skin, take them off, and place them in a container. You will practice these tasks several times in order to familiarize yourself with how to handle the ticks carefully and successfully. You will also be trained to recognize tick attachment/biting behavior, which includes cessation of crawling motion and pressing mouth parts against the subject's skin or placing head down against your skin while lifting hindmost legs off of the your skin. If you observe this behavior during the test, you will alert the attending technician, who will remove the tick immediately using a paintbrush or, if needed, tweezers. You may ask the technician for advice on how to handle the ticks at any time while you are practicing. The ticks used for this training are reared in the laboratory and free from diseases.

Visit 2

This is the day of the actual repellent study. You will first be guided to wash your lower arms with mild, low fragrance soap, rinsing them with a spray of ethyl alcohol (mixed at 35% in water), and then drying them with a clean towel. Experienced personnel will then apply repellents to one of your forearms to give even, complete coverage of the skin. The amount of repellent applied on an arm is likely to be no more than about ¼ teaspoon. Your other arm will not be treated, but will instead be used to determine whether each tick is active enough to be tested on your treated arm.

During the test, you will be seated at a laboratory table with about six other treated subjects, and a researcher or technician will lead you in handling and keeping track of the ticks, of the time, and of your tick observations. Every 15 minutes, you will test a new tick from one species first on your untreated and then on your treated arm, and report the results to your leader. You will then repeat that sequence with a tick of the other species. Together testing the two ticks will usually take between 5 and 10 minutes to complete. At times you may need to stand so that the ticks may climb upward, which is their preference.

Every 15 minutes a researcher or technician will announce the beginning of the next period for testing the treated skin. You will continue in this way until a tick of each species crosses the repellent in two of three consecutive periods, as long as you are comfortable. There will time for brief breaks to eat and use the bathroom between test periods.

When a technician indicates you are finished with the testing activity, the technician will direct you to discard your gloves and wash any applied skin area to make sure all treatment residues are removed. Using a clean towel each time, wash applied areas with cleanser, rinse with water, dry, then wash with mild alcohol solution (35% ETOH in water) rinse with water, and dry.

Deleted: Before the field testing, the subjects and researchers will gather in an area that is free of biting insects. You should not leave this area until instructed by a researcher. You will be introduced to the technicians and other researchers who will assist you and directed to ask them any questions you may have. Depending on conditions on the day of the test, limb washing, donning of protective clothing, and repellent applications to treated subjects may be completed at the laboratory prior to departure to the field site, or at the site after arrival.

A technician will guide you in washing the lower arms and/or legs with mild, low-fragrance cleanser, 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 1/2 teaspoon, and is typical of what people commonly use. You will be randomely (like the flip of a coin) chosen to receive either 20% Picaridin spray or 20% Picaridin cream. You will be given protective coveralls and gloves to prevent bites on other parts of your arms and legs, plus a head net. Vulnerable areas around wrists, elbows, ankles, and knees will be provided with extra protection.

Two experienced subjects will also participate to record the activity of biting flies 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.

At the field site, you will be given a small artists' paintbrush to use to brush off or lightly crush any biting flies that land on your skin and attempt to bite you once the test begins. A researcher or technician will show you how to use it. You will also be introduced or reintroduced 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 protecting yourself from biting insects or reporting a biting fly that lands on your skin.

After repellent application, introductions, and provision of small artists' ... [1]

RISKS / DISCOMFORTS

If at any time you feel ill, inform the Principal Investigator (or anyone else who is assisting to direct the study) immediately. 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 without penalty to your compensation. At least one qualified researcher will remain with the other test subjects if other researchers depart with an injured or ill subject.

The cream repellent will cause substantial but temporary injury to eyes on contact. The pump spray repellent will cause moderate irritation to eyes on contact. Both are 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.

If they bite you, ticks can transmit serious diseases, or cause tick paralysis. Ticks require many minutes to bite through the skin, and we do not expect them to attempt to bite you during the study. The artist's paintbrush that we will train you to use to handle ticks will also be used to remove any ticks before they bite or bury in the skin. The ticks have been screened for infectious diseases at the US Centers for Disease Control and have been determined to be free of the pathogens that cause Lyme Disease, Rocky Mountain Spotted Fever, Ehrlichiosis, and Anaplasmosis. Contact a physician and the Principal Investigator if you develop a rash within 7 days after the day of testing. The first-aid kit at the laboratory contains treatments to reduce allergic symptoms. 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 test.

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.

If you are a female subject who is tested for pregnancy, and you test positive, there is some risk of psychological stress from the surprise of the result. Only a single female technician will evaluate the results, and no record will be made of the results, to maximize your privacy by minimizing the small but present risk that other staff or subjects may become aware of the results.

Deleted: In addition, even if you have not previously had a serious skin reaction to a biting fly 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 bite. You should inform the Principal Investigator or one of his technicians if you are having such a reaction.

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In addition, there is a very 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 will be conducted in an area in which such viruses have not been detected by state health or mosquito-control agencies for at least two weeks, and at a time of year when such viruses are rarely present in mosquito populations in the test area. The risk is probably very 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 a ... [2]

Deleted: 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.

... [3]

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, or change the nature of the risks associated with participating.

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 that covers you. 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) 902-8267.
You DO NOT 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.

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) 902-8267 at any time.

If you have any questions regarding your rights as a research volunteer, please contact Kim Lerner, Chair of the Independent Investigational Review Board, Inc. at toll free 1- (877) 888-iirb (4472) between 6:00 AM and 2:00 PM, Pacific time, Monday through Friday. You can also contact the Independent Investigational Review Board, Inc. if you would like to report problems in a research study, express concerns, ask questions, request information, or provide input. The Independent Investigational Review Board is a committee established for the purpose of protecting the rights of volunteers in a research study. For more

information about your rights and role as a research participant you can visit the Research Participant section of the IIRB, Inc. website at www.iirb.com.

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 $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. Representatives from the sponsor (LANXESS Corporation), 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
You understand that you are free to withdraw from this study at any time, and you agree to inform the Principal Investigator immediately if you intend to withdraw. It is understood that your decision to participate in this study or to withdraw from this study will not influence the availability of your future medical care and will involve no penalty or loss of compensation or benefits to which you are otherwise entitled. You may withdraw from this study at any time.

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

a. His/her judgment that any condition or circumstance may jeopardize your welfare or the integrity of the study.
b. Your 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 (MM/DD/YY)	Time	**Print** Subject Name	**Sign** Subject Name
Date		**Print** Carroll-Loye Biological Research Representative	**Sign** Carroll-Loye Biological Research Representative

Copy of signed/dated consent form given to subject on (date)_____ by_____ (initials)

Independent Investigational Review Board, Inc.

Shawn King User 7/26/09 11:43 PM
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Version:
Protocol: LNX-003

APPROVED BY
Independent IRB

Signature Date

Initials: _____
Date: _____

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

Any person who is requested to consent to participate as a subject in a research study involving an 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 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 and Experimental Subject's Bill of Rights when one is required.
10. Be given the opportunity to decide to consent or not to consent to an experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision.

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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) 902-8267 at any time.

If you have any questions regarding your rights as a research volunteer, please contact Kim Lerner, Chairman of the Independent Investigational Review Board, Inc. at toll free (877) 888-IIRB (4472) between 6AM and 2PM, Pacific Time, Monday through Friday. The Independent Investigational Review Board is a committee established for the purpose of protecting the rights of volunteers in a research study.

_____ _____
Signature of Subject Date

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Signature of Witness Date

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Independent IRB

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INDEPENDENT INVESTIGATIONAL REVIEW BOARD INC.

Site Questionnaire
Additional Site to Multi-Site Study

I. GENERAL SITE INFORMATION

Protocol Number: **LNX-003**	Sponsor: **LANXESS Corporation**
Complete Study Title: **EFFICACY TEST OF KBR 3023 (PICARIDIN; ICARIDIN) - BASED PERSONAL INSECT REPELLENTS (20% CREAM AND 20% SPRAY) WITH TICKS UNDER LABORATORY CONDITIONS**	
Principal Investigator: **Scott P. Carroll, Ph.D., Carroll-Loye Biological Research**	After Hours or 24 Hour Phone Number: (emergency contact for subjects) **530-902-8267**
Sub Investigator(s): **None**	
Site Address: **711 Oak Ave., Davis CA 95616** ☒ Mail documents here	Principal Investigator's Mailing Address: (If different) ☐ Mail documents here
Regulatory/Study Coordinator: **G. K. Sangha, Ph. D.**	Phone: **913-638-3968**
Fax Number: **253-840-8047**	Main Office Phone: **913-638-3968**
Email: **sangha8@roadrunner.com**	

Is this study being conducted internationally? ☐ Yes* ☒ No
* If yes, please complete an International Addendum located under forms at www.iirb.com.

Is this study being conducted at more than one location under the oversight of the Principal Investigator?
☐ Yes* ☒ No

*If yes is the Principal Investigator affiliated with the additional site(s)? ☐ Yes ☐ No**
**If no, please complete a Multiple-Center Research Form located on our website at www.iirb.com.

If the study is being conducted at multiple locations under the same Principal Investigator, and information requested differs for each location, please complete an Additional Location Form for each additional location. (Note: This does not apply to locations only performing diagnostic testing).

II. STUDY INFORMATION You may attach copies of relevant procedures.

1. Does the Principal Investigator, Sub Investigator(s), key personnel or any of their immediate family members have a conflict of interest with the study sponsor, sponsor representatives or other study related entities as described in the Investigators' Guidebook available on our website? ☐ Yes** ☒ No*

** Checking No indicates your understanding of a conflict of interest as outlined in the Investigators Guidebook.*
***If yes, please complete the Site Conflict of Interest and Disclosure Form located under forms at www.iirb.com*

for each individual with a conflict of interest.

2. Is the language for research-related injuries listed in the submitted Informed Consent Form consistent with the Sponsor contract?

   ☒ Yes ☐ No

3. Does this study require review under U.S. Department of Health and Human Services (DHHS) standards?
   ☐Yes* ☒ No

   * If yes, is the informed consent form you are submitting considered a DHHS approved sample consent document? ☐Yes ☐ No

   * If yes, what is the site's FWA number?

III. SITE QUALIFICATIONS

4. Describe the setting(s) where the study will be conducted.
   ☒ private office ☐ research clinic ☐ hospital environment** ☐ Other **:

   **If being conducted in a hospital environment (i.e Hospital or Outpatient Surgery Center) or in another setting (i.e home, school, or lab) where administrative or corporate approval is required, please provide a copy of that facility's license/accreditation (if applicable) and/or Facility Waiver Form.

5. Describe any state or clinic policies for this site that are outside the norm of clinical research practices (i.e., legal age of consent is not 18, a separate HIV consent is required, site monitoring by the IRB is required, etc.).
   None

6. Describe the resources that are accessible to the Investigator, Sub Investigators, and staff to accommodate this research study (i.e., trained personnel that are familiar with the protocol, adequate space and storage, necessary equipment, sufficient time, etc.).
   PI & staff trained in human research practices. Our protocols are developed with direct staff knowledge and participation. Based on its technical capacities, experience and know how, Carroll-Loye has received approval to conduct such studies under onging federal and scientific and ethical oversight. We maintain a master schedule of studies, which is audited by independent QA, which shows our work density. Our schedule has always been deemed acceptable.

7. Describe the site's policies and procedures for protecting the privacy of subjects related to study visits and procedures performed (i.e., providing private interview areas and private examination space).
   Private interview and briefing rooms. Anonymous coding of results. Locked and coded storage of private information and subject data.

8. Confirm that your facility maintains the confidentiality of data and personal health information (i.e. HIPAA, HIV status, etc.) through AT LEAST the following measures (by placing check marks in each of the first 3 boxes).

   ☒ All of the study staff have agreed to not disclose any identifiable health information.
   ☒ Electronic files will only be accessible to the study staff which will require a password to access the information, or ☐ no electronic files are used.
   ☒ Paper-based records and files will be stored in a location that is secure and is only accessible to the authorized study staff.

☐ Other, explain:

9. Describe the on-site emergency equipment and rescue medications available for the subjects:
Extensive first aid equipment suitable for study risks including epipens

10. Distance between the research site and nearest hospital:
1.8 miles

11. Describe how the site will store, secure, and/or dispense investigational materials.
Stored in locked cabinet, dispensed by technicians in predetermined allocation scheme.

12. Describe the practices in place for notifying subjects of positive results of infectious diseases (i.e. HIV and hepatitis , VDRL) and reporting these results to governing agencies. Indicate a N/A if no infectious disease testing is being conducted. **N/A Ticks used in study are laboratory reared and certified disease free**

13. How long has the PI been conducting research with human subjects? **20** years **2** months

14. **HUMAN RESEARCH PARTICIPANT PROTECTION TRAINING:** Attach certificate of training for investigators. If no certificate of completion is available please include a signed note to file by the investigator attesting to completion of HRP training and include objectives and date of completion.

If no specific training has been completed access to CITI HRP Training is available through Independent Investigational Review Board, Inc. at no cost. Information about accessing the program is available in the Investigator Guidebook and through the website www.IIRB.com entering through the "Investigator Door".

15. Is the PI knowledgeable of Good Clinical Practices (GCP) 21 CFR 312, Subpart D, "Responsibilities of Sponsors and Investigators?" ☐ Yes ☒ No Knowledgeable of US EPA GLP regulations (40 CFR 160); 40 CFR 26 Subparts K, L, M; FIFRA 12(a)(2)(P)

15a. Is the PI knowledgeable of Good Clinical Practices (GCP) 21 CFR 812, Subpart E, "Responsibilities of Investigators" for device studies?" ☐ Yes ☒ No as per Question 15 above

16. Is the PI and research team knowledgeable of the ethical principles of the Belmont Report?
☒ Yes ☐ No*

** If no, please explain:*

17. Has the FDA/OHRP/EPA or any State Medical Board ever sanctioned or suspended the Principal Investigator?
☐ Yes* ☒ No **If yes, please provide a summary of the action and applicable correspondence.*

18. Within the past 3 years has the FDA/OHRP/EPA audited your site/Principal Investigator? ☐ Yes* ☒ No
**If yes, please provide a copy* of the Established Inspection Report (EIR) and any other supporting documentation.

19. Has an IRB ever terminated a study for any reason or imposed any sanctions or restrictions on the PI?
☐ Yes* ☒ No **If yes, please provide a summary of the action and applicable correspondence.*

IV. RECRUITMENT AND INFORMED CONSENT

20. Are subjects recruited from the Principal Investigator's Clinical Practice?
☐ Yes* ☒ No (Note: If yes, there must be protections in place, in light of the physician-patient relationship and trust, so that a patient will not be unduly influenced to participate as a subject in a research study).

*If yes, are any subjects categorically excluded (other than for study design purposes) from the Principal Investigator's Clinical Practice ☐ Yes** ☐ No

** If yes, please explain:

21. Are subjects recruited from a database of potential Subjects ☒ Yes* ☐ No (See Investigator's Guidebook for recommendations for database management)

*If yes, is the database comprised of only individuals who have given prior approval to be contacted?
☒ Yes ☐ No**

***If no, please explain*:

22. Other recruitment methods: ☒ None
☐ Advertising in the community* *(*advertisements Must be approved by the IIRB, Inc.)*
☐ Existing Subjects (rollover subjects, study extension)
☐ Physician Referral **
☐ Other *(please specify)*:

** HIPAA regulations prohibit physician-to-physician referral; patients must first be informed of a trial and agree to be contacted before any physician referral can be initiated.

23. Are there practices and measures in place to assure that recruitment and selection of subjects for participation in research is fair and is made without bias from social, racial, sexual and cultural institutions in society.
☒ Yes ☐ No*

**If no, please explain*:

24. Will you be conducting telephone screenings? ☐ Yes* ☒ No

* If yes, do you have policies in place to ensure the following regarding telephone screenings:
☐ The potential subject will be asked if they would like their information kept on file or in a database in order to be contacted for future studies.
☐ If the potential subject does not want their information stored on file or in a database, the site will properly destroy (i.e. delete electronic files, shred documents, etc.) the information collected during the telephone screening.
☐ Only authorized personnel will have access to the database or records on file pertaining to personal health information.
☐ The database or on file records will be stored in a secure location.
☐ Other:

25. What are community attitudes toward research in your local community?
☐ Neutral ☒ Positive ☐ Negative*

* *If negative, please attach explanation.*

26. 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? ☐ Yes* ☒ No

*If yes, please explain how coercion will be avoided.

27. Indicate the approximate demographics of your site's anticipated subject population:

4% African American **74**% Caucasian **7**% Hispanics **12** % Asian **3**% Other

52 % Male **48** % Female

28. Do you have access to a population that would allow recruitment of the required number of subjects?

☒ Yes ☐ No* * If No, explain:

29. Will you be enrolling subjects who do not speak English in this study? ☐ Yes* ☒ No

*If Yes, indicate the translation needed: ☐ Spanish ☐ Other:

Note: A certified translation must be reviewed by IIRB, Inc. prior to use.

30. If you are enrolling subjects that do not speak English is there a person available and fluent in the translated study documents requested during the informed consent process and duration of the study?

☐Yes ☐No ☒N/A

31. Does a person fluent in the translation review the approved translated study documents prior to being used to ensure that the translation is consistent with any local dialect? ☐ Yes ☐ No ☒ N/A

32. Does this study require you to recruit subjects from vulnerable study populations or other populations that require additional safeguards? ☐ Yes ☒ No*

* If no, do you anticipate enrolling any of the populations listed above anyway?
☐ Yes ☒ No, If no, skip question #33. If yes, *provide justification for inclusion of these populations if they are being enrolled.*

33. Indicate which populations you anticipate enrolling (either because the protocol requires enrollment or demographics of your site) and attach a copy of your consenting procedures that are relevant to additional safeguards you have in place to protect the rights and welfare of each selected population. *Checking a box below indicates your understanding of how to protect that group as outlined in the Investigator's Guidebook available on our website.*

☐ Educationally Disadvantaged/Illiterate	☐ Members of the Armed Forces
☐ Nursing Home Resident	☐ Patients with incurable disease
☐ Patients in emergency situations	☐ Economically Disadvantaged
☐ Mentally disabled	☐ Employees (Site/Sponsor/CRO)
☐ Children*	☐ Disabled
☐ Pregnant women**	☐ Other:

** If children will be enrolled, submit a completed Research Involving Children Addendum.*
*** If you are enrolling pregnant women, complete the Pregnant Women and Fetuses Addendum.*

Note: The IIRB, Inc. does not review research studies with prisoners as research subjects.

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

☒ Principal Investigator ☐Sub Investigator ☐Study Coordinator ☒ Other: **Carroll-Loye Biological Research technician NIH or CITI certified as trained in protecting human subject research participants**

35. Describe the qualifications and training of the individuals communicating information to the subject or the legally authorized representative during the consent process (i.e., trained in consenting procedures, and that the information is provided in a language that the subject or the representative understands well). **Personnel obtaining consent are CITI or NIH certified. All consenting is conducted in a language that the subject understands well.**

Attach your consenting process/procedures. If you do not have written operating procedures that adequately address the following questions, answer questions 36 through 43 listed below.

36. Describe how the investigator or designee will ensure the language is understandable to the subject, based on the subject's education level and language ability. **Subjects are all college educated in English in the United States**

37. Describe where the consenting process will take place (i.e., private room, quiet area, etc.).**Consent takes place in a private office. Other people are excluded from the office during consenting.**

38. Describe the steps taken to minimize the possibility of coercion or undue influence (i.e. giving sufficient opportunity and privacy to voluntarily consider whether to participate). **All potential participants are screened or re-screened for suitability for each test in a private, one-on-one conversation held at the Carroll-Loye Biological Research office. The Exclusion Criteria are exercised by asking each candidate to address them in the interview. The interviewer encourages candidates to ask questions and ask for clarification at any time during the meeting and in all activities that follow. To candidates that pass screening the interviewer 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 review. 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 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 or are students in the 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.

39. Will the subject be given the consent form to bring home and discuss with their family? ☒ Yes ☐ No*
    * If no, explain:

40. Describe how the investigator or designee will obtain the legally effective informed consent of the subject or the subject's legally authorized representative. **In meeting with the PI or trained/certified personnel, IIRB-approved ICF is signed by both parties.**

41. Describe the content of the information communicated to the subject or the representative during the consent process (i.e., specific to not include any exculpatory language through which the subject or the legally authorized representative is made to waive or appear to waive any of the subject's legal rights). **The language used during the consenting process indicates that the investigator will be responsible for any health issues or injuries that result from participation in the study. It is fully consistent with the ICF language.**

42. Describe how you evaluate subjects' capacity, understanding, and informed consent or assent (i.e., ask open ended questions, have subject repeat information about what has been discussed, etc.) **Subjects are college students or college graduates, or professionals (teachers, lab technicians, etc.). We ask them to discuss their level of outdoor activity, experience with biting insects, allergies, physical condition, and also require them to assist in taking their physical measurements and to understand why we are taking those measurements. We frequently repeat that they should ask questions. Any subjects not giving coherent responses, or responses that reflect an understanding of the basic plan and goals of the study, are withdrawn from consideration.**

43. Will subjects with legally authorized representatives (LAR) be enrolled? ☐ Yes* ☒ No
    *If yes, how will you verify who constitutes an LAR in your state?

    ☐ legal counsel ☐ sponsor/CRO ☐ state law reference material ☐ state law codes and statutes
    ☐ other:

V. PAYMENT TO SUBJECT(S)

44. Will subjects be paid for participation in this study? ☒ Yes ☐ No

45. What is the amount per visit? **$20**
Note: If amount per visit differs, indicate each amount or attach a separate schedule.

46. What is the total payment: **Depends on hours**

47. When will payment occur? **On last visit** *(i.e. at each visit, at the last visit, within 2 weeks of the last visit).*

48. Will subjects be paid for additional unscheduled visits? ☐ Yes* ☒ No If yes, indicate amount: _____

Note: Payments must be made on at least a yearly basis for studies with durations longer than 12 months, and must be within the guidelines listed in the Investigator's Guidebook.

VI. SITE SPECIFIC INFORMED CONSENT FORM INFORMATION

49. Is there any site specific language needed for the Informed Consent Form (other than PI name, contact information, and payment information). ☒ Yes* ☐ No

If yes, please specify the additional wording below, or attach a copy of the ICF with the site specific information included.* **Uncertain - ICF attached

INVESTIGATOR ACKNOWLEDGMENT

On behalf of all of the investigators listed on page 1, I agree:

- that the responses provided on this Site Questionnaire are true and accurate to the best of my knowledge and I agree to notify the Independent Investigational Review Board, Inc. of any changes in the research activities.
- to report any problems that require prompt reporting.
- not to make any changes in the research without IIRB, Inc. approval.
- that study personnel are familiar with the study and are educated on human research programs including underlying ethical principles from the Belmont Report.
- that the research-related injury statement in the submitted informed consent form, or informed consent form template on file is consistent with the sponsor contract in order to ensure the rights and welfare of subject with injuries during participation in this study.
- that either an Investigator or designee will orally explain the Informed Consent Form to all prospective subjects before obtaining their signed informed consent form and will see that no subject is coerced to participate in a research study.
- that all study records and related documentation are accessible to an authorized representative of the Independent Investigational Review Board, Inc. at reasonable times and in a reasonable manner.

I have been informed that the Investigator's Guidebook is located on the IIRB, Inc. website, and agree to operate in compliance with the information within the Guidebook. 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, and all state and federal regulations.

Name and title of individual completing Site Questionnaire: **Shawn King, Director of Operations**	Phone Number: **916-832-9593**

Print Name of Principal Investigator: Scott P. Carroll	
Signature of Principal Investigator: Scott P Carr	**Date:** 26 July 2009

Please contact the IIRB, Inc., if you have any questions regarding this questionnaire at 954.327.0778

INDEPENDENT INVESTIGATIONAL REVIEW BOARD INC.

Study setup form

PROTOCOL TITLE: (LNX-003) EFFICACY TEST OF KBR 3023 (PICARIDIN; ICARIDIN) - BASED PERSONAL INSECT REPELLENTS (20% CREAM AND 20% SPRAY) WITH TICKS UNDER LABORATORY CONDITIONS

SPONSOR:LANXESS CORPORATION

Sponsor Contact Information

Contact/Title: Dr. G. K. Sangha, Ph. D. Regulatory Affairs Consultant | Phone/Fax:913-638-3968/253-840-8047 | Email:sangha8@roadrunner.com

Address: GKS International, 11411 Porter Ranch Drive #105, Northridge, CA 91326

CRO:

CRO Contact Information

Contact/Title: | Phone/Fax: | Email:

Address:

STUDY STATUS

If the IIRB, Inc. is acting as the Central IRB on a study, please check Multiple Sites. If the study protocol is being conducted at only one site, or at more than one site but the IIRB, Inc, is not acting as the Central IRB, please check single site.

Single Site Multiple Sites

INFORMED CONSENT PROCEDURES

Do changes to the Informed Consent Form need to be reviewed by any of the parties involved (i.e. Sponsor, CRO) prior to review by the IIRB, Inc.?

No Yes, if yes please indicate party Sponsor CRO Other:

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

Use translations Services through IIRB, Inc. (Americo Gomez)
We will provide our own Spanish Translations

*Please note that Americo Gomez serves as an independent contractor of Independent Investigational Review Board, Inc. Americo Gomez is a certified translator with a long standing working relationship with the IIRB, Inc. and his credentials are recognized and found acceptable by the IIRB, Inc. Due to being a separate entity, you will receive a separate invoice for his translating services.

Additional questions regarding translation services can be sent to AGomez5634@aol.com.

* Please note that translations for other languages must be arranged for by the site, sponsor, or CRO. In addition, appropriate supporting documentation (i.e. certified letter of translation and curriculum vitae of

certified translator) is necessary.	
MAILING INSTRUCTIONS: address for Sites do NOT need to be listed – just identify as "sites" (so that we have on file who receives copies of documents and who gets originals!)	
Originals to: ☐ Sponsor ☐ CRO ☒ Site	Send by (choose one): ☒ FedEX ☐ UPS ☐ DHL ☐ USPS ☐Other:
Address: Carroll-Loye Biological Research, 711 Oak Ave., Davis CA 95616	Account #: 177-484-318
Copies to: ☐ Sponsor ☐ CRO ☐ Site	Send by (choose one): ☐ FedEX ☐ UPS ☐ DHL ☐ USPS ☐ Email ☐Other:
Address:	Account #: Email Address:
Notes: Please include any additional instructions for mailing. Include if copies of routine correspondence get sent to CRO/Sponsor, sent US Mail, etc.	
BILLING INSTRUCTIONS: ☐ Sponsor ☐ CRO ☒ Site ☐ Other:	
Billing Contact Information ☒ **same as listed above**	

Contact/Title:	Phone/Fax:	Email:
Address:		
Purchase Order # (if applicable):		
TODAY'S DATE:26 JULY 2009		

from	**Shawn King** <sbkingster@gmail.com>
to	Yesenia Crespo <ycrespo@iirb.com>, Robert Roogow <rroogow@iirb.com>
cc	Scott P Carroll <spcarroll@ucdavis.edu>
date	Mon, Jul 27, 2009 at 8:10 AM
subject	Study LNX-003 full signature page
mailed-by	gmail.com

Hi Robert and Yesenia,

Please find enclosed the completed protocol approval page for our study LNX-003 as referred to in my email sent earlier today.

Thank you.

Best, Shawn King
--
Director of Operations
Carroll-Loye Biological Research

8 Protocol Approval Signatures

Scott P. Carroll, Ph.D.
Study Director

July 26, 2009
Date

for Stanley C. Ostosky
Stanley C. Ostosky
Head of Regulatory Affairs
LANXESS Corporation

July 27, 2009
Date

G. K. Sangha, Ph. D.
Study Monitor

July 27, 2009
Date

from **Yesenia Crespo** <YCrespo@iirb.com>
to Shawn King <sbkingster@gmail.com>
date Mon, Jul 27, 2009 at 12:32 PM
subject RE: Initial Submission Protocol LNX-003

Dear Shawn everything looks OK except that the Site Questionnaire is a multi site questionnaire and not a single site questionnaire. Could you please complete the correct one and re-send it to us prior to tomorrows meeting.

Regards,
Yesenia Crespo
Project Leader
Independent Investigational Review Board INC.

from **Shawn King** <sbkingster@gmail.com>
to Yesenia Crespo <ycrespo@iirb.com>
cc Robert Roogow <rroogow@iirb.com>,
Scott P Carroll <spcarroll@ucdavis.edu>
date Mon, Jul 27, 2009 at 9:45 PM
subject LNX-003 Single Site Questionnaire
mailed-by gmail.com

Hi Yesenia,

Thanks for being willing to take our Protocol submission on such short notice!

Please find enclosed our submission of the Single-Site Questionnaire form for our study LNX-003 as you requested earlier today.

Please contact me by phone if additional documentation is required for the board review.

Thanks again!

Best, Shawn King

-
Director of Operations
Carroll-Loye Biological Research

INDEPENDENT INVESTIGATIONAL REVIEW BOARD INC.

Site Questionnaire
Single Site Study

I. GENERAL SITE INFORMATION	
Protocol Number: **LNX-003**	Sponsor: **LANXESS Corporation**
Complete Study Title: **EFFICACY TEST OF KBR 3023 (PICARIDIN; ICARIDIN) - BASED PERSONAL INSECT REPELLENTS (20% CREAM AND 20% SPRAY) WITH TICKS UNDER LABORATORY CONDITIONS**	
Principal Investigator:**Scott P. Carroll, Ph.D., Carroll-Loye Biological Research**	After Hours or 24 Hour Phone Number: (emergency contact for subjects) **530-902-8267**
Sub Investigator(s):**None**	
Site Address:**711 Oak Ave., Davis CA 95616** ☒ Mail documents here	Principal Investigator's Mailing Address: (If different) ☐ Mail documents here
Regulatory/Study Coordinator:**G. K. Sangha, Ph. D.**	Phone:**913-638-3968**
Fax Number:**253-840-8047**	Main Office Phone:**913-638-3968**
Email:**sangha8@roadrunner.com**	

Is this study being conducted internationally? ☐ Yes* ☒ No
* If yes, please complete an International Addendum located under forms at www.iirb.com.

Is this study being conducted at more than one location under the oversight of the Principal Investigator?
☐ Yes* ☒ No

*If yes is the Principal Investigator affiliated with the additional site(s)? ☐ Yes ☐ No**
**If no, please complete a Multiple-Center Research Form located on our website at www.iirb.com.

If the study is being conducted at multiple locations under the same Principal Investigator, and information requested differs for each location, please complete an Additional Location Form for each additional location. (Note: This does not apply to locations only performing diagnostic testing).

II. STUDY INFORMATION You may attach copies of relevant procedures.

1. Does this study require review under U.S. Department of Health and Human Services (DHHS) standards?
☐Yes* ☒ No

   * If yes, is the informed consent form you are submitting considered a DHHS approved sample consent document? ☐Yes ☐ No

* If yes, what is the site's FWA number?

2. Does this study have an investigational new drug (IND) number?

☐ Yes, Indicate number: _____

☒ No IND is required, please explain why: **N/A Study is to test insect repellents, not drugs or medications of any kind**

If this study has an IND number indicate which documentation of it you are submitting (one must be checked):

☐ Industry sponsored protocol with IND.
☐ Letter from FDA.
☐ Letter from industry sponsor.
☐ Other document and/or communication verifying the IND.

Note: The Investigator's Brochure is not adequate documentation of an IND number.

Is the IND in the FDA 30 day waiting period? ☐ Yes ☐ No

3. Does this research involve an Investigational Device? ☐ Yes* ☒ No

*If yes, please attach one of the following:
☐ FDA letter granting an IDE for the proposed use, or
☐ Letter from sponsor explaining why the investigation is exempt from the IDE requirements under 21 CFR 812.2(c)(1)-(7), or
☐ Letter from sponsor explaining why the device meets criteria for non-significant risk device determination. (meets the abbreviated IDE requirements under 21 CFR 812.2(b)).

4. Has this study for this site been reviewed by another IRB? ☐ Yes* ☒ No

*If yes, include a copy of the IRB's letter (i.e., approval, disapproval, deferred), and when appropriate a study closeout letter from the other IRB.

5. Does the Principal Investigator, Sub Investigator(s), key personnel or any of their immediate family members have a conflict of interest with the study sponsor, sponsor representatives or other study related entities as described in the Investigators' Guidebook available on our website? ☐ Yes** ☒ No*

** Checking No indicates your understanding of a conflict of interest as outlined in the Investigators Guidebook.*
***If yes, please complete the Site Conflict of Interest and Disclosure Form located under forms at www.iirb.com for each individual with a conflict of interest.*

6. Is the language for research-related injuries listed in the submitted Informed Consent Form consistent with the Sponsor contract?

☒ Yes ☐ No

7. Will the Investigator act as the sponsor of this research study? ☐ Yes* ☒ No

* If yes, does the Investigator agree to conduct research in accordance to the regulatory responsibilities of a sponsor as listed in Investigator's Guidebook? ☐ Yes ☐ No**

** If no, explain. **independent lab testing repellents for sponsor, LANXESS Corp.**

8. Indicate how data and subject safety monitoring is conducted at the site (i.e., initiation and monitoring visits, monitoring of laboratory results, general subject safety mechanisms).

Study is a single-day experiment, with no "on-going" monitoring over time. Data quality and compliance with protocol directives, including safety management, are verified by an independent Quality Assurance Unit (inspector), who reports to management and provides a written certification of compliance for inclusion in the research report resulting from the study. This Quality Assurance inspector is present during the single-day experimental trial to observe all study related activities and is charged with notifying management and the Study Director of any observed problems as they occur, as well as documenting those problems.

Subject safety is further guaranteed by candidate screening procedures that include the use of exclusion criteria, and Medical Management Practices (see Protocol LNX-003, attached, for detail on Medical Management Practices). For example, in this study, the exclusion criteria help screen out subjects that, as individuals, may be unusually sensitive to the Test Materials, to the target organisms in the repellency test, or to physical conditions of the trial, or belong to well-defined vulnerable populations not required for insect repellent testing.

III. SITE QUALIFICATIONS

9. Describe the setting(s) where the study will be conducted.

☒ private office ☐ research clinic ☐ hospital environment** ☐ Other **:

**If being conducted in a hospital environment (i.e Hospital or Outpatient Surgery Center) or in another setting (i.e home, school, or lab) where administrative or corporate approval is required, please provide a copy of that facility's license/accreditation (if applicable) and/or Facility Waiver Form.

10. Describe any state or clinic policies for this site that are outside the norm of clinical research practices (i.e., legal age of consent is not 18, a separate HIV consent is required, site monitoring by the IRB is required, etc.).

None

11. Describe the resources that are accessible to the Investigator, Sub Investigators, and staff to accommodate this research study (i.e., trained personnel that are familiar with the protocol, adequate space and storage, necessary equipment, sufficient time, etc.).

PI & staff trained in human research practices. Our protocols are developed with direct staff knowledge and participation. Based on its technical capacities, experience and know how, Carroll-Loye has received approval to conduct such studies under onging federal and scientific and ethical oversight. We maintain a master schedule of studies, which is audited by independent QA, which shows our work density. Our schedule has always been deemed acceptable.

12. Describe the site's policies and procedures for protecting the privacy of subjects related to study visits and procedures performed (i.e., providing private interview areas and private examination space).

Private interview and briefing rooms. Anonymous coding of results. Locked and coded storage of private information and subject data.

13. Confirm that your facility maintains the confidentiality of data and personal health information (i.e. HIPAA, HIV status, etc.) through AT LEAST the following measures (by placing check marks in each of the first 3 boxes).

☒ All of the study staff have agreed to not disclose any identifiable health information.

☒ Electronic files will only be accessible to the study staff which will require a password to access the information, or ☐ no electronic files are used.
☒ Paper-based records and files will be stored in a location that is secure and is only accessible to the authorized study staff.
☐ Other, explain:

14. Describe the on-site emergency equipment and rescue medications available for the subjects:
Extensive first aid equipment suitable for study risks including epipens

15. Distance between the research site and nearest hospital:
1.8 miles

16. Describe how the site will store, secure, and/or dispense investigational materials.
Stored in locked cabinet, dispensed by technicians in predetermined allocation scheme.

17. Describe the practices in place for notifying subjects of positive results of infectious diseases (i.e. HIV and hepatitis , VDRL) and reporting these results to governing agencies. Indicate a N/A if no infectious disease testing is being conducted. **N/A Ticks used in study are laboratory reared and certified disease-free**

18. How long has the PI been conducting research with human subjects? **20** years **2** months

19. **HUMAN RESEARCH PARTICIPANT PROTECTION TRAINING:** Attach certificate of training of the investigators. If no certificate of completion is available please include a signed note to file by the investigators attesting to completion of HRP training and include objectives and date of completion.

If no specific training has been completed access to CITI HRP Training is available through Independent Investigational Review Board, Inc. at no cost. Information about accessing the program is available in the Investigator Guidebook and through the website www.IIRB.com entering through the "Investigator Door".

20. Is the PI knowledgeable of Good Clinical Practices (GCP) 21 CFR 312, Subpart D, "Responsibilities of Sponsors and Investigators?" ☐ Yes ☒ No Knowledgeable of US EPA GLP regulations (40 CFR 160); 40 CFR 26 subparts K, L, m; FIFRA 12 (a)(2)(p)

20a. Is the PI knowledgeable of Good Clinical Practices (GCP) 21 CFR 812, Subpart E, "Responsibilities of Investigators" for device studies? ☐ Yes ☒ No As per Question 20 above

21. Is the PI and research team knowledgeable of the ethical principles of the Belmont Report?
☒ Yes ☐ No*

** If no, please explain:*

22. Has the FDA/OHRP/EPA or any State Medical Board ever sanctioned or suspended the Principal Investigator?
☐ Yes* ☒ No **If yes, please provide a summary of the action and applicable correspondence.*

23. Within the past 3 years has the FDA/OHRP/EPA audited your site/Principal Investigator?
☐ Yes* ☒ No

**If yes, please provide a copy* of the Established Inspection Report (EIR) and any other supporting documentation.

24. Has an IRB ever terminated a study for any reason or imposed any sanctions or restrictions on the PI?
☐ Yes* ☒ No **If yes, please provide a summary of the action and applicable correspondence.*

IV. RECRUITMENT AND INFORMED CONSENT

25. Are subjects recruited from the Principal Investigator's Clinical Practice?

☐ Yes* ☒ No

(Note: If yes, there must be protections in place, in light of the physician-patient relationship and trust, so that a patient will not be unduly influenced to participate as a subject in a research study).

*If yes, are any subjects categorically excluded (other than for study design purposes) from the Principal Investigator's Clinical Practice ☐ Yes** ☐ No

** *If yes, please explain:*

26. Are subjects recruited from a database of potential Subjects ☒ Yes* ☐ No (See Investigator's Guidebook for recommendations for database management)

*If yes, is the database comprised of only individuals who have given prior approval to be contacted?
☒ Yes ☐ No**

***If no, please explain*:

27. Other recruitment methods: ☒ None

☐ Advertising in the community* *(*advertisements Must be approved by the IIRB, Inc.)*
☐ Existing Subjects (rollover subjects, study extension)
☐ Physician Referral **
☐ Other *(please specify):*

** HIPAA regulations prohibit physician-to-physician referral; patients must first be informed of a trial and agree to be contacted before any physician referral can be initiated.

28. Are there practices and measures in place to assure that recruitment and selection of subjects for participation in research is fair and is made without bias from social, racial, sexual and cultural institutions in society.

☒ Yes ☐ No*

**If no, please explain*:

29. Will you be conducting telephone screenings? ☐ Yes* ☒ No

* If yes, do you have policies in place to ensure the following regarding telephone screenings:
☐ The potential subject will be asked if they would like their information kept on file or in a database in order to be contacted for future studies.
☐ If the potential subject does not want their information stored on file or in a database, the site will properly destroy (i.e. delete electronic files, shred documents, etc.) the information collected during the telephone screening.
☐ Only authorized personnel will have access to the database or records on file pertaining to personal health information.
☐ The database or on file records will be stored in a secure location.
☐ Other:

30. What are community attitudes toward research in your local community?
☐ Neutral ☒ Positive ☐ Negative*

** If negative, please attach explanation.*

31. 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? ☐ Yes* ☒ No

*If yes, please explain how coercion will be avoided.

32. Indicate the approximate demographics of your site's anticipated subject population:

4% African American **74**% Caucasian **7**% Hispanics **12** % Asian **3**% Other

52 % Male **48** % Female

33. Do you have access to a population that would allow recruitment of the required number of subjects?

☒ Yes ☐ No* * If No, explain:

34. Will you be enrolling subjects who do not speak English in this study? ☐ Yes* ☒ No

*If Yes, indicate the translation needed: ☐ Spanish ☐ Other:

Note: A certified translation must be reviewed by IIRB, Inc. prior to use.

35. If you are enrolling subjects that do not speak English is there a person available and fluent in the translated study documents requested during the informed consent process and duration of the study?

☐Yes ☐No ☒N/A

36. Does a person fluent in the translation review the approved translated study documents prior to being used to ensure that the translation is consistent with any local dialect? ☐ Yes ☐ No ☒ N/A

37. Does this study require you to recruit subjects from vulnerable study populations or other populations that require additional safeguards? ☐ Yes ☒ No*

* If no, do you anticipate enrolling any of the populations listed above anyway?
☐ Yes ☐ No, If no, skip question #38. If yes, *provide justification for inclusion of these populations if they are being enrolled.*

38. Indicate which populations you anticipate enrolling (either because the protocol requires enrollment or demographics of your site) and attach a copy of your consenting procedures that are relevant to additional safeguards you have in place to protect the rights and welfare of each selected population. *Checking a box below indicates your understanding of how to protect that group as outlined in the Investigator's Guidebook available on our website.*

☐ Educationally Disadvantaged/Illiterate	☐ Members of the Armed Forces
☐ Nursing Home Resident	☐ Patients with incurable disease
☐ Patients in emergency situations	☐ Economically Disadvantaged
☐ Mentally disabled	☐ Employees (Site/Sponsor/CRO)
☐ Children*	☐ Disabled
☐ Pregnant women**	☐ Other:

** If children will be enrolled, submit a completed Research Involving Children Addendum.*

*** If you are enrolling pregnant women, complete the Pregnant Women and Fetuses Addendum.*

Note: The IIRB, Inc. does not review research studies with prisoners as research subjects.

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

☐ Principal Investigator ☐Sub Investigator ☐Study Coordinator ☒ Other: **Carroll-Loye Biological Research technician NIH or CITI certified as trained in protecting human subject research participants**

40. Describe the qualifications and training of the individuals communicating information to the subject or the legally authorized representative during the consent process (i.e., trained in consenting procedures, and that the information is provided in a language that the subject or the representative understands well). **Personnel obtaining consent are CITI or NIH certified. All consenting is conducted in a language that the subject understands well.**

Attach your consenting process/procedures. If you do not have written operating procedures that adequately address the following questions, answer questions 41 through 48 listed below.

41. Describe how the investigator or designee will ensure that the language is understandable to the subject, based on the subject's education level and language ability. **Subjects are all college educated in English in the United States**

42. Describe where the consenting process will take place (i.e., private room, quiet area, etc.).**Consent takes place in a private office. Other people are excluded from the office during consenting.**

43. Describe the steps taken to minimize the possibility of coercion or undue influence (i.e. giving sufficient opportunity and privacy to voluntarily consider whether to participate). **All potential participants are screened or re-screened for suitability for each test in a private, one-on-one conversation held at the Carroll-Loye Biological Research office. The Exclusion Criteria are exercised by asking each candidate to address them in the interview. The interviewer encourages candidates to ask questions and ask for clarification at any time during the meeting and in all activities that follow. To candidates that pass screening the interviewer 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 review. 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 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 or are students in the 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.

44. Will the subject be given the consent form to bring home and discuss with their family? ☒ Yes ☐ No*
    * If no, explain:

45. Describe how the investigator or designee will obtain the legally effective informed consent of the subject or the subject's legally authorized representative. **In meeting with the PI or trained/certified personnel, IIRB-approved ICF is signed by both parties.**

46. Describe the content of the information communicated to the subject or the representative during the consent process (i.e., specific to not include any exculpatory language through which the subject or the legally authorized representative is made to waive or appear to waive any of the subject's legal rights). **The language used during the consenting process indicates that the investigator will be responsible for any health issues or injuries that result from participation in the study. It is fully consistent with the ICF language.**

47. Describe how you evaluate subjects' capacity, understanding, and informed consent or assent (i.e., ask open ended questions, have subject repeat information about what has been discussed, etc.) **Subjects are college students or college graduates, or professionals (teachers, lab technicians, etc.). We ask them to discuss their level of outdoor activity, experience with biting insects, allergies, physical condition, and also require them to assist in taking their physical measurements and to understand why we are taking those measurements. We frequently repeat that they should ask questions. Any subjects not giving coherent responses, or responses that reflect an understanding of the basic plan and goals of the study, are withdrawn from consideration.**

48. Will subjects with legally authorized representatives (LAR) be enrolled? ☐ Yes* ☒ No
    *If yes, how will you verify who constitutes an LAR in your state?

    ☐ legal counsel ☐ sponsor/CRO ☐ state law reference material ☐ state law codes and statutes
    ☐ other:

V. PAYMENT TO SUBJECT(S)

49. Will subjects be paid for participation in this study? ☒ Yes ☐ No

50. What is the amount per visit? **$20**
Note: If amount per visit differs, indicate each amount or attach a separate schedule.

51. What is the total payment: **Depends on hours**

52. When will payment occur? **On last visit** *(i.e. at each visit, at the last visit, within 2 weeks of the last visit).*

53. Will subjects be paid for additional unscheduled visits? ☐ Yes* ☒ No If yes, indicate amount: _____

Note: Payments must be made on at least a yearly basis for studies with durations longer than 12 months, and must be within the guidelines listed in the Investigator's Guidebook.

VI. SITE SPECIFIC INFORMED CONSENT FORM INFORMATION

54. Is there any site specific language needed for the Informed Consent Form (other than PI name, contact information, and payment information). ☒ Yes* ☐ No

If yes, please specify the additional wording below, or attach a copy of the ICF with the site specific information included.* **Uncertain - ICF attached

INVESTIGATOR ACKNOWLEDGMENT

On behalf of all of the investigators listed on page 1, I agree:

- that the responses provided on this Site Questionnaire are true and accurate to the best of my knowledge and I agree to notify the Independent Investigational Review Board, Inc. of any changes in the research activities.
- to report any problems that require prompt reporting.
- not to make any changes in the research without IIRB, Inc. approval.
- that study personnel are familiar with the study and are educated on human research programs including underlying ethical principles from the Belmont Report.
- that the research-related injury statement in the submitted informed consent form, or informed consent form template on file is consistent with the sponsor contract in order to ensure the rights and welfare of subject with injuries during participation in this study.
- that either an Investigator or designee will orally explain the Informed Consent Form to all prospective subjects before obtaining their signed informed consent form and will see that no subject is coerced to participate in a research study.
- that all study records and related documentation are accessible to an authorized representative of the Independent Investigational Review Board, Inc. at reasonable times and in a reasonable manner.

I have been informed that the Investigator's Guidebook is located on the IIRB, Inc. website, and agree to operate in compliance with the information within the Guidebook. 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, and all state and federal regulations.

Name and title of individual completing Site Questionnaire: **Shawn King, Director of Operations**	Phone Number: **916-832-9593**

Print Name of Principal Investigator: Scott P. Carroll	
Signature of Principal Investigator: Scott Carroll	Date: 27 July 2009

Please contact the IIRB, Inc., if you have any questions regarding this questionnaire at 954.327.0778

from **Yesenia Crespo** <YCrespo@iirb.com>
to Shawn King <sbkingster@gmail.com>
date Fri, Jul 31, 2009 at 6:21 AM
subject LNX003

Please see attached the word format of the approved consent form. You should receive the hard copy original by Monday.

Regards,
Yesenia Crespo
Project Leader
Independent Investigational Review Board INC.

INFORMED CONSENT AUTHORIZATION TO PARTICIPATE AS A RESEARCH STUDY SUBJECT

Title of Study: LNX-003 EFFICACY TEST OF KBR 3023 (PICARIDIN; ICARIDIN) - BASED PERSONAL INSECT REPELLENTS (20% CREAM AND 20% SPRAY) WITH TICKS UNDER LABORATORY CONDITIONS

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Principal Investigator: Scott P. Carroll, Ph.D.
Carroll-Loye Biological Research
711 Oak Avenue
Davis, CA 95616
(530) 902-8267

Site of Investigation: Carroll-Loye Biological Research
711 Oak Avenue, Davis, CA 95616

Sponsor: LANXESS Corporation

Participant's Name: _____

INTRODUCTION

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 request, we will also provide you with a copy of the study Protocol, which details all the procedures of the study, and contains details about product safety. 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 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. 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 cream and pump spray formulations, works against two types of ticks. The information gained from the study will assist in developing these repellents for commercial marketing. During the study, we will test the insect repellents against ticks in a laboratory.

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The sponsor, LANXESS Corporation, 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 invited to participate in this research study because you are a male or female, read and speak English, consider yourself to be in good physical condition and are 18-55 years old.

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If you are a female of child-bearing potential, you cannot be pregnant or breastfeeding. Using an over-the-counter (OTC) pregnancy kit supplied by a technician, you will perform a pregnancy test at the laboratory on the day of any study visit in which repellent will be applied or in which you will be exposed to biting insects. Your test results will be verified by a female technician experienced in making that assessment. 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. If you decide to withdraw from the study after taking the pregnancy test you do not need to show a positive result.

RESTRICTIONS

- You must not be a student or employee of the Principal Investigator.
- You must not be hypersensitive (allergic) to tick bites, or phobic of ticks.
- You must not be sensitive to any of the test product ingredients, or allergic to common cosmetics.
- You must regularly spend time in outdoor settings.
- You must be able to see and remove ticks that come in contact with your skin.
- 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. To meet this restriction, you may need to purchase fragrance-free cosmetics prior to the test days. If you do, you will be reimbursed for your expenses.
- You must refrain from smoking or consuming alcoholic beverages after 9 p.m. the night before and throughout the tests.

NUMBER OF SUBECTS PARTICIPATING

Up to about 23 subjects will be enrolled at this single-site 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

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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	Visit 2
1. Orientation visit	X	
2. Field study visit		X
Total time	2-2.5 hours	8-16 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

Within 30 days before the second visit (in which we will test the repellents against ticks), 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 will also be shown how handle ticks on your skin with a small artist's paintbrush. This training and practice will take about ½ hour.

The total time for Visit 1 activities will be about 2-2.5 hours.

Visit 2 for the Tick Repellent Test

The study will also require a second visit to the same laboratory. This second visit will most likely require approximately 12 hours of your time. However, it may require as few as about 4 hours or many as about 16 hours, depending on how long the repellents remain effective. Bathrooms are available, and meals, drinks and snacks will be provided.

STUDY PROCEDURES

Visit 1

At the laboratory, a researcher will measure the length and circumference of your forearm. If you have participated in a Carroll-Loye Biological Research study within the last two years, and were measured for that study, we will use your on-file limb measurements unless, when asked, you indicate that you think you have gained or lost weight or muscle mass on your limbs since the previous measurements were taken.

You will also be given a verbal orientation to the activities of the test day, with an opportunity to ask the researcher questions or share your concerns about any aspect of the research activities.

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At the laboratory, you will spend about 30 minutes practicing handling ticks in the laboratory in preparation for the repellent study. A technician will show you how to catch the ticks, place them on your skin, take them off, and place them in a container. You will practice these tasks several times in order to familiarize yourself with how to handle the ticks carefully and successfully. You will also be trained to recognize tick attachment/biting behavior, which includes cessation of crawling motion and pressing mouth parts against the subject's skin or placing head down against your skin while lifting hindmost legs off of the your skin. If you observe this behavior during the test, you will alert the attending technician, who will remove the tick immediately using a paintbrush or, if needed, tweezers. You may ask the technician for advice on how to handle the ticks at any time while you are practicing. The ticks used for this training are reared in the laboratory and free from diseases.

Visit 2

This is the day of the actual repellent study. You will first be guided to wash your lower arms with mild, low fragrance soap, rinsing them with a spray of ethyl alcohol (mixed at 35% in water), and then drying them with a clean towel. Experienced personnel will then apply repellents to one of your forearms to give even, complete coverage of the skin. The amount of repellent applied on an arm is likely to be no more than about ¼ teaspoon. You will be randomly (like a flip of a coin) assigned to receive either 20% Picaridin Spray or 20% Picaridin Cream. Your other arm will not be treated, but will instead be used to determine whether each tick is active enough to be tested on your treated arm.

During the test, you will be seated at a laboratory table with about six other treated subjects, and a researcher or technician will lead you in handling and keeping track of the ticks, of the time, and of your tick observations. Every 15 minutes, you will test a new tick from one species first on your untreated and then on your treated arm, and report the results to your leader. You will then repeat that sequence with a tick of the other species. Together testing the two ticks will usually take between 5 and 10 minutes to complete. At times you may need to stand so that the ticks may climb upward, which is their preference.

Every 15 minutes a researcher or technician will announce the beginning of the next period for testing the treated skin. You will continue in this way until a tick of each species crosses the repellent in two of three consecutive periods, as long as you are comfortable. There will time for brief breaks to eat and use the bathroom between test periods.

When a technician indicates you are finished with the testing activity, the technician will direct you to discard your gloves and wash any applied skin area to make sure all treatment residues are removed. Using a clean towel each time, wash applied areas with cleanser, rinse with water, dry, then wash with mild alcohol solution (35% ETOH in water) rinse with water, and dry.

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RISKS / DISCOMFORTS

If at any time you feel ill, inform the Principal Investigator (or anyone else who is assisting to direct the study) immediately. 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 without penalty to your compensation. At least one qualified researcher will remain with the other test subjects if other researchers depart with an injured or ill subject.

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The cream repellent will cause substantial but temporary injury to eyes on contact. The pump spray repellent will cause moderate irritation to eyes on contact. Both are 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.

If they bite you, ticks can transmit serious diseases, or cause tick paralysis. Ticks require many minutes to bite through the skin, and we do not expect them to attempt to bite you during the study. The artist's paintbrush that we will train you to use to handle ticks will also be used to remove any ticks before they bite or bury in the skin. The ticks have been screened for infectious diseases at the US Centers for Disease Control and have been determined to be free of the pathogens that cause Lyme Disease, Rocky Mountain Spotted Fever, Ehrlichiosis, and Anaplasmosis. Contact a physician and the Principal Investigator if you develop a rash within 7 days after the day of testing. The first-aid kit at the laboratory contains treatments to reduce allergic symptoms. 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 test.

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.

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If you are a female subject who is tested for pregnancy, and you test positive, there is some risk of psychological stress from the surprise of the result. Only a single female technician will evaluate the results, and no record will be made of the results, to maximize your privacy by minimizing the small but present risk that other staff or subjects may become aware of the results.

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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, or change the nature of the risks associated with participating.

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 that covers you. 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) 902-8267.

You DO NOT waive any of 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.

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) 902-8267 at any time.

If you have any questions regarding your rights as a research participant, please contact Kim Lerner, Chair of the Independent Investigational Review Board, Inc. at toll free 1- (877) 888-iirb (4472) between 6:00 AM and 2:00 PM, Pacific time, Monday through Friday. You can also contact the Independent Investigational Review Board, Inc. if you would like to report problems in a research study, express concerns, ask questions, request information, or provide input. The Independent Investigational Review Board is a committee established for the

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purpose of protecting the rights of participants in a research study. For more information about your rights and role as a research participant you can visit the Research Participant section of the IIRB, Inc. website at www.iirb.com.

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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 $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. Representatives from the sponsor (LANXESS Corporation), 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
You understand that you are free to withdraw from this study at any time, and you agree to inform the Principal Investigator immediately if you intend to withdraw. It is understood that your decision to participate in this study or to withdraw from this study will not influence the availability of your future medical care and will involve no penalty or loss of compensation or benefits to which you are otherwise entitled. You may withdraw from this study at any time.

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

a. His/her judgment that any condition or circumstance may jeopardize your welfare or the integrity of the study.
b. Your 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.

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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 any of my legal rights by signing this Informed Consent Form. I shall receive a copy of the signed Informed Consent Authorization.

Date (MM/DD/YY) _____ Time **Print** Subject Name _____ **Sign** Subject Name

Date _____ **Print** Carroll-Loye Biological Research Representative _____ **Sign** Carroll-Loye Biological Research Representative

Copy of signed/dated consent form given to subject on (date)_____ by_____ (initials)

Independent Investigational Review Board, Inc.
Approved: 7/28/09

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EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

Any person who is requested to consent to participate as a subject in a research study involving an 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 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 and Experimental Subject's Bill of Rights when one is required.
10. Be given the opportunity to decide to consent or not to consent to an experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision.

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) 902-8267 at any time.

If you have any questions regarding your rights as a research volunteer, please contact Kim Lerner, Chairman of the Independent Investigational Review Board, Inc. at toll free (877) 888-IIRB (4472) between 6AM and 2PM, Pacific Time, Monday through Friday. The Independent Investigational Review Board is a committee established for the purpose of protecting the rights of volunteers in a research study.

_____ _____
Signature of Subject Date

_____ _____
Signature of Witness Date

APPROVED BY
Independent IRB

_____ 7/28/09
Signature Date

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From **Yesenia Crespo** <YCrespo@iirb.com>
to Shawn King <sbkingster@gmail.com>
cc Scott P Carroll <spcarroll@ucdavis.edu>
date Fri, Jul 31, 2009 at 11:49 AM
subject LNX003

Please see attached

Regards,
Yesenia Crespo
Project Leader
Independent Investigational Review Board INC.

Ed. Note: The documents enclosed with this email are pages 28-38 of this submission

from **Shawn King** <sbkingster@gmail.com>
to Robert Roogow <rroogow@iirb.com>
cc Yesenia Crespo <ycrespo@iirb.com>,
Scott P Carroll <spcarroll@ucdavis.edu>
date Mon, Aug 3, 2009 at 10:15 AM
subject Study LNX-003 Administrative Letter
mailed-by gmail.com

Hi Robert,

Please find enclosed an administrative letter concerning our study protocol LNX-003. Please provide an expedited review, and email a scanned PDF of IIRB, Inc. response to the review as soon as that document is available. If you have any questions or concerns, please contact me at your earliest convenience.

Thank you!

Best, Shawn King

Director of Operations
Carroll-Loye Biological Research

Carroll-Loye Biological Research

711 Oak Avenue Davis, California 95616 Tel (530) 902-8267 http://www.carroll-loye.com/

3 August 2009

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

Administrative Letter, Carroll-Loye Protocol LNX-003

Dear Mr. Roogow,

This letter clarifies and corrects a clerical error in the study Protocol as noted by IIRB, Inc. in their letter to the Study Director dated July 30, 2009.

The Informed Consent Form (Page 3, Visit 1 for Orientation, first sentence) states subject training and orientation will occur within 30 days of the repellency test date. The Protocol states periods of both 30 days (Page 7, Section 1.3.2, Line 219) and 60 days (Page 22, Section 4.8.1, Line 762). The latter figure is a clerical transcription error.

Section 4.8.1, Line 762 (header) is now corrected to read: “Within 30 days preceding Test Day”.

Scott P. Carroll, PhD
Study Director

from **Robert Roogow** <RRoogow@iirb.com>
to Scott P Carroll <spcarroll@ucdavis.edu>,
Shawn King <sbkingster@gmail.com>
date Tue, Aug 4, 2009 at 11:57 AM
subject Meeting minutes

Dear Shawn and Scott,

I have attached the minutes for your files. You are already in receipt of our current policies and membership roster as they have not changed since June 1, 2009. Please let me know if you need anything additional.

Regards,
Robert

Robert Roogow, MS, CIM
Chief Operating Officer
Independent Investigational Review Board, Inc.

Tuesday, July 28, 2009
MINUTES

ATTENDANCE:

PRESENT	ALSO PRESENT
Shari Somerstein, RPh	Robert Lettman, Esq.
Edward Wiederhorn	
Julie Blasingim, alternate for George Garbarino	ABSENT
David Wells, MD, alternate for Marcos Rejtman, DO	Frances Conway, RN
Rabbi Akiva Mann	
Kim Lerner	NOT PRESENT
	George Garbarino
GUEST	Marcos Rejtman, DO
Katy Kysela, Director of Research, IRB Liaison	

I. CALL TO ORDER

The meeting was called to order at 10:12 AM, by Chairman, Kim Lerner. The meeting was held at 6738 West Sunrise Blvd., Suite 102, Plantation, FL 33313. Quorum was determined to be present and all attendees affirmed that no significant financial or non-financial conflicts of interest existed with review of any of the items listed on the agenda.

II. APPROVAL OF THE 7/21/2009 MINUTES (The order of the Minutes does not reflect the order in which they were reviewed.)

The minutes of the meeting held 7/21/2009 were reviewed and unanimously approved as reviewed. Robert Lettman abstained from voting.

III. REVIEW PROTOCOLS

III a. STUDY INITIAL APPROVALS

D (Protocol LNX-003) EFFICACY TEST OF KBR 3023 (PICARIDIN; ICARIDIN) - BASED PERSONAL INSECT REPELLENTS (20% CREAM AND 20% SPRAY) WITH TICKS UNDER LABORATORY CONDITIONS

Principal Investigator: Scott P. Carroll, PhD

Approval Clinical Research;

- Informed Consent Form version 7/28/2009
- California Experimental Subject's Bill of Rights
- Research Protocol version 7/27/09
- Site Questionnaire

Motion was made, seconded and the Committee approved the Investigator(s), Informed Consent Form, California Experimental Subject's Bill of Rights and Research Protocol for the above noted research study. The Site Questionnaire was reviewed and accepted.

A discrepancy was noted in the protocol related to the screening time period before the test day. On page 7 of the protocol it states within 30 days before repellent efficacy testing, subjects will be trained. However on page 22 section 4.8.1 of the protocol, it states within 60 days preceding test day, candidate screening and subject consenting and orientation will occur.

Risk

The following comments were made by the board:

- The IRB determined that risks to subjects are minimized by appropriate inclusion/exclusion criteria, repellent active ingredient has a low acute and chronic risk profile established through experimentation and history of consumer use and is registered by the FDA, subject training to avoid tick biting and available medical management in the event of a tick bite, subjects will be teamed by groups for mutual observation and experienced technical personnel will

be present at all times for assistance, use of laboratory-reared ticks that are certified disease-free, testing area temperature and humidity controlled to remain within human comfort zones, testing area free of tripping hazards and adjacent rest area provided with food, beverages and water, seating and private restroom facilities. Privacy and confidentiality are maintained during pregnancy testing for female subjects including use of a female researcher to observe test results and non-recording of test results.

The IRB reviewed the description of risks and benefits in the submitted documentation and determined that the information in the submitted documentation justified the determination that the risks are minimized and that the risks are justified in relations to the anticipated benefits.

Subject Selection
The IRB reviewed the description of subject selection in the protocol and determined that the information in the protocol justified the determination that subject selection is equitable.

Consent Process
The IRB reviewed the description of the consent process in the submitted documentation and determined that the information provided justified the determination that the consent process is appropriate.

Documentation of Consent
The IRB reviewed the description of the procedures for documentation of consent in the protocol and the submitted Informed Consent Form and determined that documentation of consent is appropriate.

Data Safety Monitoring
The IRB reviewed the description of the data safety monitoring plan in the protocol and determined that the information in the protocol and submitted documentation justified the determination that the plan is appropriate.

Privacy & Confidentiality
The IRB reviewed the description of provisions for privacy and confidentiality in the submitted documentation and determined that the information in the protocol justified the determination that the provisions are appropriate.

Vulnerable Populations
The IRB determined that no vulnerable populations are anticipated in this research.

The Committee recommended that changes be made to the Informed Consent Form. The Informed Consent Form is approved as revised. The approved Informed Consent Form is identified as Version 7/28/2009 and stamped, “Approved 7/28/2009”. The Informed Consent Form contains all regulatory required consent elements. The California Experimental Subject’s Bill of Rights is approved. The approved California Experimental Subject’s Bill of Rights is stamped, “Approved 7/28/2009”.

Based on the nature of the study and the risks to the subjects, the approval is granted for a 12 month period, with a progress report required prior to continued approval. Identified questions and concerns were discussed, addressed and documented in the file. See Approval letter for Investigator’s responsibilities and file for supporting documents.

The results of the voting for the action taken was as follows: 6 Votes for; 0 Votes against; 0 Abstained

from **Shawn King** <sbkingster@gmail.com>
to Robert Roogow <RRoogow@iirb.com>
date Tue, Aug 4, 2009 at 9:55 PM
subject Re: Meeting minutes
mailed-by gmail.com

Thanks Robert. The HRPP plan document we have on file is dated October 27, 2008. Is a more recent version available?

Best, Shawn King

Director of Operations
Carroll-Loye Biological Research

from **Robert Roogow** <RRoogow@iirb.com>
to Shawn King <sbkingster@gmail.com>
date Wed, Aug 5, 2009 at 6:15 AM
subject RE: Meeting minutes

I thought that I sent you the 6/1/2009 version the beginning of June. I have attached it here with the new Membership Roster. Let me know if you need anything else.

Regards,
Robert

Robert Roogow, MS, CIM
Chief Operating Officer
Independent Investigational Review Board, Inc.

Ed. Note: The HRPP Plan document and Membership Roster for IIRB, INC. are included as separate files with this subission.

from **Robert Roogow** <RRoogow@iirb.com>
to Shawn King <sbkingster@gmail.com>
date Wed, Aug 5, 2009 at 7:14 AM
subject HRPP plan

Shawn,

Please let me know if you got the HRPP plan. I sent it to you this morning but I have gotten complaints from other clients it was to large and not going through and I was not getting a bounce back message.

Robert Roogow, MS, CIM
Chief Operating Officer
Independent Investigational Review Board, Inc.

from **Yesenia Crespo** <YCrespo@iirb.com>
to Shawn King <sbkingster@gmail.com>
date Wed, Aug 5, 2009 at 7:31 AM
subject RE: Study LNX-003 Administrative Letter

Please see attached

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

Kim Lerner
Chairman

Anita McSharry, R.N.
President

DATE: August 04, 2009

TO: Scott P. Carroll, PhD
Principal Investigator

FROM: Authorized Signatory
Independent Investigational Review Board, Inc.

SUBJECT: Administrative Letter dated 8/3/2009;

PROTOCOL: LNX-003

The Independent Investigational Review Board, Inc. had an opportunity to review the above referenced Administrative Letter for the above noted research study. The Administrative Letter clarified and corrected a clerical error in the study Protocol as requested by the IRB. It is noted that orientation will occur within 30 days of the test date. This submission met the criteria for a minor change in previously approved research and was reviewed under expedited review procedures.

The Administrative Letter is approved. The Administrative Letter does not require a change to the consent form.

Thank you for your cooperation.

KL/AMS/yc/rr:

from	**Shawn King** <sbkingster@gmail.com>
to	Robert Roogow <RRoogow@iirb.com>
cc	Yesenia Crespo <ycrespo@iirb.com>, Scott P Carroll <spcarroll@ucdavis.edu>
date	Wed, Aug 5, 2009 at 7:58 AM
subject	Re: HRPP plan
mailed-by	gmail.com

Hi Robert,

Yes, thank you! I had no problem with the enclosures. I have also received IIRB, INC's response, sent by Yesenia this morning, to the Administrative Letter we submitted on Monday August 3. I believe our documentation is complete for the time being.

Best, Shawn King

Director of Operations
Carroll-Loye Biological Research