**PROJECT NUMBER**
**0108-433-0161**

**GUIDELINE DATA REQUIREMENT**
**OPPTS 810.3700**

**PROTOCOL TITLE**
# EVALUATION OF THE EFFICACY OF KBR 3023 (Picaridin; Icaridin)- BASED PERSONAL INSECT REPELLENTS (20% CREAM and 20% SPRAY) AGAINST STABLE FLIES IN THE LABORATORY

**STUDY DIRECTOR**
**William J. Gaynor**

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

**TESTING FACILITY**
**ICR, Inc.**
1330 Dillon Heights Avenue
Baltimore, MD 21228-1199

## STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS

No claim of confidentiality is made for any information contained in this study on the basis of its falling within the scope of FIFRA Sec. 10 (d) (1) (A), (B), or (C). No supplemental claim of confidentiality is made for any information in this study on the basis of FIFRA Sec. 10(a) or (b).

Company: LANXESS Corporation

Company Representative: G. K. Sangha, PhD

Signature: GK Sangha Date: 2/7/08

## GOOD LABORATORY PRACTICES COMPLIANCE STATEMENT

This is not a study containing original data; it does not meet Good Laboratory Practice as set forth in 40 CFR Part 160.

Study Director: William J Gaynor 2/7/08
William J. Gaynor Date

Submitter William J Gaynor 2/7/08
William J. Gaynor Date

Sponsor: G K Sangha 2/7/08
G. K. Sangha PhD Date
LANXESS Corporation

## TABLE OF CONTENTS

**EIRB APPROVED DOCUMENTS**

**Essex Institutional Review Board, Inc.**
121 Main Street • Lebanon, New Jersey 08833
Telephone (908) 236-7735 • Fax (908) 236-2027
www.essexirb.com

February 5, 2008

William J. Gaynor,
Insect Control & Research, Inc.
1330 Dillon Heights Avenue
Baltimore, MD 21228

Dear Mr. Gaynor:

The Essex Institutional Review Board, Inc. reviewed the LANXESS Corporation clinical research project, "Evaluation of the Efficacy of KBR 3023 (Picaridin; Icaridin)- Based Personal Insect Repellents (20% Cream and 20% Spray) Against Stable Flies in the Laboratory" (G4330108001A382, 1/21/08, Rev. 2/1/08).

The Protocol (dated 1/21/08) reviewed by a full board, was conditionally approved on January 28, 2008. The Revised Protocol (dated 2/1/08) was **approved on February 4, 2008.** The Essex Institutional Review Board, Inc. has determined that the proposal meets the IRB requirements for safety and ethical standards. Approval to conduct the **study expires on February 3, 2009** based on the degree of risk.

Your Informed Consent – Dose Determination and Informed Consent – Repellent Test (both dated 2/1/08) reviewed by a full board, were approved on February 4, 2008. The Telephone Recruitment Script (dated 2/1/08) was also approved on February 4, 2008.

Your Research Site located at 1330 Dillon Heights Avenue, Baltimore, MD was approved on February 5, 2008. Approval for this **site expires on February 3, 2009** contingent upon the continuing annual review and approval of the protocol by February 3, 2009.

Risks to subjects were determined to be reasonable and minimized, based on review of the study design, anticipated results, Investigator's Brochure (if it was submitted), reports of any data and safety monitoring (if available) and balancing research versus therapeutic activities and potential benefits to the participants. Recruitment practices in the selection of participants must be equitable and fair.

Essex requests that you forward a study summary, including adverse reactions, within 90 days of study termination. In any event, reports must be made at intervals not exceeding one year. Any serious, unexpected or unanticipated experiences must be reported to the Board promptly. Enclosed is our brochure detailing your responsibilities associated with this research study.

The Essex Institutional Review Board is in compliance with the federal regulations of the National Institute of Health and Office of Human Research Protection (OHRP) effective August 19, 1991 (45 CFR 46). The Board is also in compliance with the federal regulations of the Food and Drug Administration effective July 27, 1981, and with all amendments thereto, contained in Title 21 of the Code of Federal Regulations, Parts 50 and 56. The OHRP Assurance Number is 1742. A Statement of Compliance and Board Member listing are attached for your files. Access to information about the policies and procedures of Essex Institutional Review Board will be readily available upon request at any time.

Sincerely,

Glenn P. Lambert, MD

Glenn P. Lambert, MD, FAAP
Chairman

klr

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0108-433-0161

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**EVALUATION OF THE EFFICACY OF KBR 3023 (Picaridin; Icaridin)- BASED PERSONAL INSECT REPELLENTS (20% CREAM and 20% SPRAY) AGAINST STABLE FLIES IN THE LABORATORY**

**PROTOCOL VERSION DATE**
February 1, 2008

**PROPOSED LABORATORY INITIATION DATE**

TBD
**PROPOSED LABORATORY CONDUCT COMPLETION DATE**
TBD

**STUDY DIRECTOR**
William J. Gaynor

**STUDY ASSOCIATES**
Charles Cornell, Timothy Foard, Niketas Spero, Gloria Stevens and Fouad Zgidou

**SPONSOR REPRESENTATIVE**
**G.K. Sangha**

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ICR, Inc.
1330 Dillon Heights Avenue
Baltimore, MD 21228-1199

## TABLE OF CONTENTS

# EVALUATION OF THE EFFICACY OF KBR 3023 (Picaridin; Icaridin)- BASED PERSONAL INSECT REPELLENTS (20% CREAM and 20% SPRAY) AGAINST STABLE FLIES IN THE LABORATORY

## 1. INTRODUCTION

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 for safety, low skin penetration, 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). LANXESS is the study sponsor.

Icaridin (US EPA registration name Picaridin), the current common name, was developed under the Code Name KBR 3023 and the registered trade name 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. Despite this, Picaridin and KBR 3023 will be used henceforth as these names have become the most widely used ones in the U.S.

## 2. OBJECTIVE OF THE STUDY

The objective of the study is to determine the mean protection time from bites by stable flies provided by the test articles under laboratory conditions to confirm this hypothesis.

## 3. HYPOTHESIS

Two repellent products (205 formulations of All-Family Insect Repellent Spray and All-Family Insect Repellent Cream and referred to as "test articles" and "test products' henceforth) are expected to provide 8 hours or greater than 8 hours of personal protection from stable flies (also referred to as "flies") in a laboratory test. (also referred to as "study").

## 4. STUDY RATIONALE

ICR Inc. ("ICR"), located at 1330 Dillon Heights Avenue, Baltimore MD 21228-1199, will conduct the proposed test at its laboratory. This will evaluate the efficacy of two 20% KBR 3023-based insect repellent products (KBR 3023 All-Family Insect Repellent Spray and KBR 3023 All-Family Insect Repellent Cream) against laboratory-raised stable flies. Laboratory studies, such as the one proposed, have been considered by regulatory authorities and the scientific community to be a reliable method for testing the performance of topically-applied insect repellent products. Under EPA's OPPTS Guideline 810.3700 ("Product Performance of Skin-Applied Repellents of Insect and Other Arthropods") human efficacy study data is required to support registration of insect repellent products to substantiate the product label claims.

The products (20% Formulations of All-family Insect Repellent Spray and All-Family Insect Repellent Cream) are conditionally registered by EPA pending conduct of new efficacy data including stable flies. However, no testing of 20% KBR 3023 products has been conducted against biting flies in the US or Europe. A 7.5% KBR-3023 is the highest level tested in a field and a cage study conducted in Europe, but it involved three species which do not occur in the U.S., as well as stable flies, (unpublished LANXESS study 06-LX-04, 2007). The study duration was limited to only four hours and the details of the data are not available. Therefore, this study is planned to determine the efficacy of the two 20% KBR 3023 products in a cage test.

Stable flies can transmit animal-related diseases, but very rarely transmit any diseases which afflict people. The pest status of these flies as they relate directly to humans is almost entirely due to their painful bite and annoyance. They are rapid fliers and easily elude the swatting hand or rolled newspaper. The data generated from the study will provide consumers with an alternative and effective choice of a repellent.

## 5. RISKS AND BENEFITS

The main risks associated with the proposed study are the potential for allergic or irritation responses to the test materials, and exposure to biting flies. The potential for disease transmission is almost non-existent. Risk to the subjects health and safety are not likely either during or after the study as described below:

Most people do not exhibit a skin reaction to stable fly bites other than feeling transient pain. ICR's stable flies have been raised in the laboratory for many generations and have not been exposed to human blood sources (they are fed *in vitro* on bovine blood). Therefore the potential risk of contracting an insect-borne disease will be essentially zero, leaving irritation from stable fly bites as the only hazard from these insects.

Picaridin has low acute toxicity and long term studies showed no adverse effects of concern by the use of the product. The product has been registered in 33 countries and over years of use showed that it can be used safely (the safety profile of the product, as provide by the sponsor, is presented in Appendix V). The 20% concentration of the active ingredient in the two All-family formulations proposed for the study is higher than the marketed and EPA-registered formulation. The product will be used according to current label and risks associated with the use during the study are not anticipated.

The inert ingredients used in the two products have been used extensively in the cosmetic industry without adverse events. Subjects with a history of reaction to insect bites, insect repellents, and skin care products will be excluded from the study. Further, the subjects will be closely monitored during both the dose-determination phase of the study, as well as during the repellent phase of the study, for signs of reactions. Subjects will be especially closely monitored during the dose-determination study when they apply the products to their forearms (see *Dose Determination*). Prompt medical attention will be sought should any adverse reaction be experienced.

## 6. STUDY OVERVIEW

There will be two phases of the study: the dose determining phase and repellent phase.

*a) Dose Determination Phase*
The test doses will be determined before the repellent test by allowing human subjects to apply both products to their forearms. These subjects will be instructed to apply the products as they would normally when applying a repellent, the only criterion being that the amount applied is what they would choose. ICR will measure the weights applied. Each subject will apply each product three times. The means of these application weights will be used to treat the subjects in the repellent test. This is detailed below under section 11 (page 17)

b) *Repellent Test Phase*
ICR plans to test 12 human subjects, with their left forearms treated with the cream product and their right forearms with the spray products, for repellency to groups of 25 caged stable flies. Subjects will expose their treated forearms to these flies for 5 minutes every half hour for 10 hours, or until they receive a confirmed bite on both arms, whichever occurs first. The times to the first confirmed bite will be the protection time for each product on each subject. Ten hours will allow a reliable documentation of an 8-hour claim. This phase is detailed below under section 20 (page 22).

## 7. TEST ARTICLE (PRODUCT) NOMENCLATURE, INFORMATION AND DISPOSITION

a) *The table below summarizes the identity of the two test articles.*

| Active Ingredient | Product Name | EPA Reg. No. | Application Rate | ICR Code |
|---|---|---|---|---|
| **20% Picaridin*** | **KBR 3023 All-Family Insect Repellent Cream** | **39967-50** | ≤4 mg/cm$^{2*}$ ≤1000 mg/250cm$^{2*}$ | **A** |
| **20% Picaridin*** | **KBR 3023 All-Family Insect Repellent Spray** | **39967-53** | ≤4 mg/cm$^{2*}$ ≤1000 mg/250cm$^{2}$ | **B** |

* 2-(2-hydroxyethyl)-1piperidinecarboxylic acid 1-methylpropyl ester

b) Upper limit for treatment dose
The amount to be applied will be determined in the dose determination phase of the study, but in no case will it exceed 4 mg/cm$^2$ without additional review and approval by EIRB as this is the maximum application rate that they will be provided for the purpose of hazard assessment.

c) MSDS
A Material Safety Data Sheet (MSDS) shall be provided for each test, control, and/or reference sample, which will include any hazardous information of the test articles. The percentage of all active ingredients and any hazardous constituents must be included in all MSDSs.

d) *Chain of custody letter*
A chain of custody letter must accompany all test, control, and/or reference test articles.

- **e)** *Test Article Characterization*
  Sample characterization is a key GLP (Good Laboratory Practices) requirement detailed in 40 CFR Part 160. The sponsor is solely responsible for conducting the complete test article, control sample, and any reference sample characterizations according to GLPs, and for providing ICR with this characterization data prior to the experimental start date of this study. This characterization must define the identity, strength, purity, and composition of the batch(es) or lot(s) of test articles. If any of the test, control and/or reference test articles are currently available for consumer use and/or purchased in the marketplace, ICR will need the same characterization information provided by the sponsor prior to the experimental start date of this study. If documentation of this characterization is not provided prior to the experimental start date, this will be noted as a

non-compliance item in the GLP compliance statement. This sample characterization information will be retained in the ICR archives, and a statement identifying this location will be included in the final report. LANXESS has agreed to provide this information.

f) *Sponsor Responsibilities*
The study sponsor shall provide the study director with the entire compositions of the test articles prior to the experimental start date.
The stability of the test and, when applicable, control, and/or reference test articles shall be determined by the sponsor prior to the experimental start date. When relevant to the conduct of this study, the solubility of each test, control, and/or reference sample shall be determined prior to the experimental start date.

Methods of synthesis, fabrication, or derivation of the test, control, and/or reference test articles shall be documented by the sponsor, and the location of such documentation shall be specified by the sponsor in a letter to the Study director. LANXESS has done this.

The stability of test, control, and/or reference test articles stored under the test site conditions shall be known for all studies. LANXESS has this information.

g). *Return of Unused Test Articles*
All unused portions of the test articles will be returned to the sponsor within 30 days of the final report being sent to the sponsor. The sponsor will be responsible for all costs for the return of the test articles, including any costs associated with hazardous materials shipping.

## 8. TEST ORGANISM

*a) Introduction*
The stable fly (*Stomoxys calcitrans* L) resembles the better known house fly (*Musca domestica* L.). Close inspection reveals that it has the piercing mouthparts (proboscis) of a blood-feeder rather than the enlarged, rounded tip of the house fly's mouth parts (which is used for swabbing up food). Stable flies are obligate blood feeders with both sexes relying upon this diet (unlike mosquitoes in which only the females will take blood meals). Stable flies attack cattle, horses and other farm animals, household pets and people. Their bite is painful, often more so than that of a mosquito. The itching and swelling which often follows a mosquito bite, is however, usually lacking after stable fly bites. They are restless biters and will often interrupt a meal to fly elsewhere. As noted below stable flies rarely, if ever, transmit diseases to humans but they have been implicated in diseases to animals (e.g. anthrax and the equine nematode parasites of the genus *Habronema).*

*b) Origin of ICR Stable Fly Colony*

The source of ICR's stable fly colony is the colony maintained by USDA Gainesville, Florida. Pupae from this colony were obtained in November 2006. Prior to this ICR had maintained a stable fly colony originating from USDA Kerrville Texas in 1983.

c) Stable Flies for Repellent Study

Groups of twenty-five adult, mixed sex, 3-10 day old stable flies will be aspirated from stock cages and released into each cage for each 5- minute exposure period. These test stable flies will have been fed 10% sucrose rather than their normal diet of citrated bovine blood. They will have had no sucrose for twenty-four hours prior to the study and they will have not have received a blood meal.

## 9. TEST CAGES

a) *Description*

There will be six test cages and two subjects will use each cage. The aluminum test cages (constructed by ICR) measure 2 x 2 x 2 feet with two sleeved entry ports on each of two opposite sides of the cage (4 entry ports/cage). The cage sides (except for the sleeved entrances) and top are screened. The floor is lined with a reflective material to facilitate observation of stable flies landing on the under surfaces of the forearms. A bar runs across the center of the cage to serve as a hand rest. See figures 1 and 2 below.

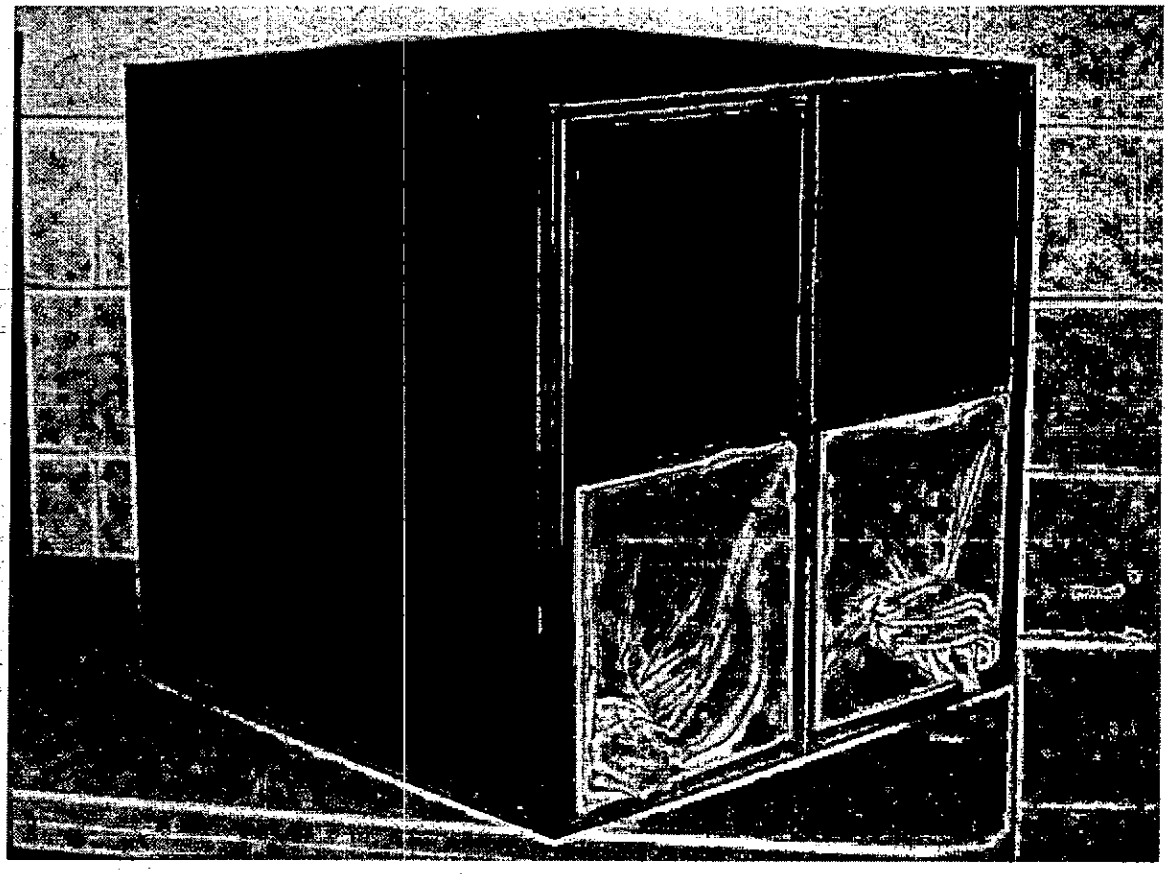


Figure 1. Test cages showing entrance sleeves closed

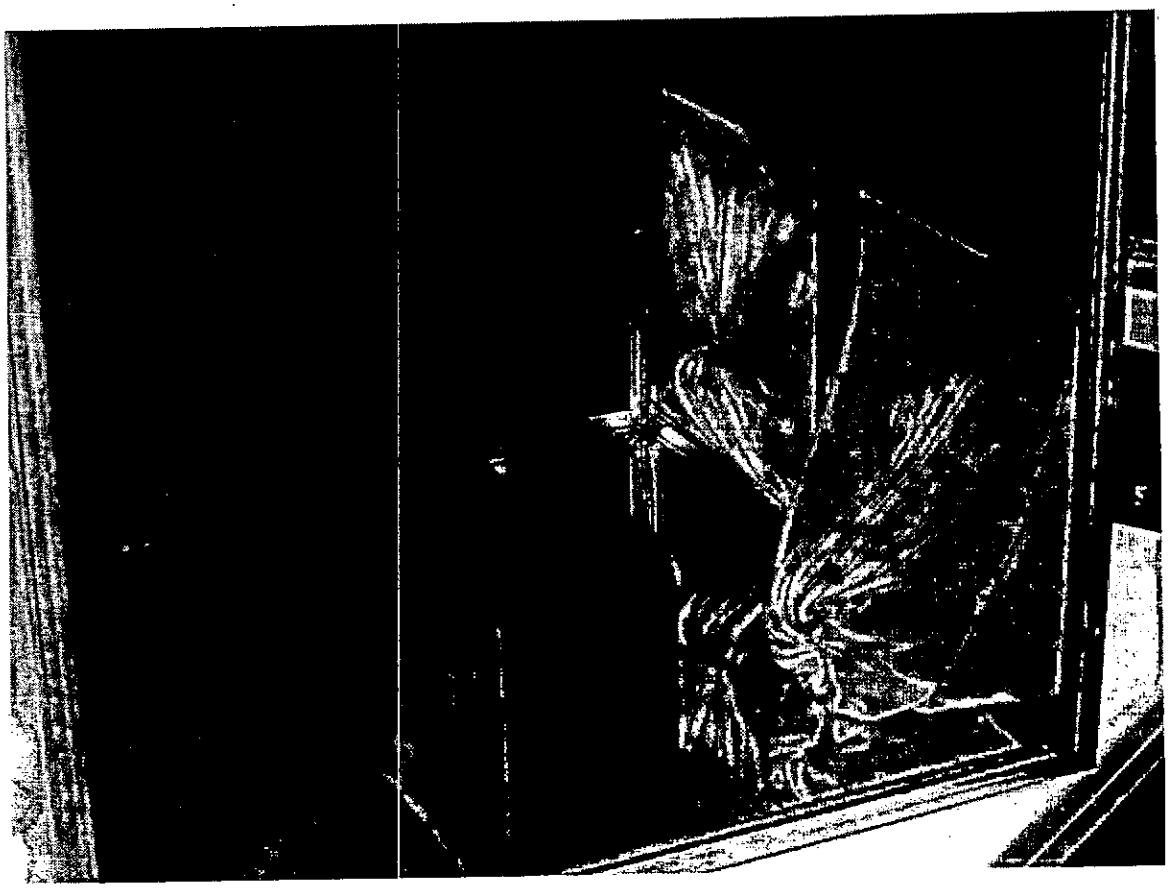


Figure 2. Test cages show hand rest bar and reflecting mirror.

*b) Evidence for Lack of Interference between Two Subjects' treated Forearms in Cages*
ICR has tested pairs of subjects in these cages with mosquitoes or stable flies for over 30 years and has not seen any evidence of interference between different treatments. Evidence of this lack of effect is provided by incomplete treatments or abrasion of treated forearms. In the former, if a 250 $cm^2$ area of a forearm is incompletely treated such that areas of skin are left untreated, stable flies will promptly land on these areas, despite the close proximity of treated skin. Similarly, ICR has seen cases where subjects have accidentally rubbed their treated forearms against their sides or another object, removing some of the product. Stable flies will often land on these abraded areas before the nearby unabraded areas.

## 10. USE OF HUMAN SUBJECTS

### a) Introduction

There are currently no viable alternatives to using human subjects to determine the efficacy of insect repellents. Under the Federal Insecticide, Fungicide and Rodenticide Act ("FIFRA"), EPA requires that efficacy data collected from human studies be submitted to register for insect repellents. These data must substantiate any public health protection claims made on the product's labeling. Specifically, data are required to both substantiate the repellency of specific insect pests and inform the user how long the products will repel the pests on the label.

While there is an economic incentive to the sponsor of the study to offer a new insect repellent alternative to consumers, such products must benefit consumers or these products will not be purchased or used. It is important to bring new insect repellent products to market so that consumers have alternatives that are effective, acceptable and convenient to use. The products to be tested in this study have been formulated to provide protection from stable flies and to be easy to apply, pleasant to use and offer alternatives to those containing other repellent active ingredients, such as DEET.

ICR will evaluate repellency based on protection from bites while conducting laboratory studies to try to minimize discomfort to the test subjects. Efficacy is defined as the Protection Time (PT). The PT is the time interval between the application of the repellent and the First Confirmed bite (FCB). A stable fly inserts its proboscis into the subjects' skin – an act which is both felt by the subject and observed by an ICR staffer. The FCB is a bite which is followed by another bite within 30 minutes.

This study is intended for submission to EPA to support an insect repellent label claim for stable flies. The results obtained from the study will enable the product to be used worldwide if repellency is demonstrated.

### b) Justification for use of human subjects

Human subjects are required for this study because there are no satisfactory substitute models for testing insect repellents. EPA recognizes this in its draft OPPTS Guideline 810.3700 which require testing of repellents on human subjects. While there has been experimental work on product repellency using animal models, such as mice and guinea pigs, the data are not a sufficiently reliable predictor of performance on humans.
It needs to be noted that animal testing has its own set of ethical concerns, including the impossibility of obtaining informed consent from the animal subjects.

**c) Recruiting pool**

ICR is located in Baltimore County, Maryland. According to the 2000 Census, the racial makeup of Baltimore County 74.39% white, 20.10% black or Afro-American, 0.25% Native American, 3.17% Asian, 0.03% Pacific Islander, 0.62% from other races, and 1.43% from two or more races.

**d) ICR's Pool of Candidate Subjects and Plans for Representative ness**

ICR's current pool of potential subjects are all white. Afro-Americans and North Africans have participated in previous studies. For the proposed stable fly test, ICR will look for recruits from the Afro-American community, as well as from the white majority population to correct this slight imbalance.

**e) Selection Criteria**

*Inclusion Criteria:*

| | |
|---|---|
| Number: | 12 test subjects and one negative control subject needed |
| Sex: | Male or Female |
| Age: | 18 to 70 |
| Race: | No exclusions |
| Literacy: | Must be able to read, speak, and understand English |

*Exclusion Criteria*:

1. Test subjects cannot participate if they are pregnant or breastfeeding.
2. Test subjects cannot be an employee or a relative of an employee of ICR Inc., the sponsor, or any other interested party.
3. Test subjects must follow the requirements of the study as explained to them.
4. Test subjects must not be known to be unduly sensitive to stable fly bites (this is not an exclusion from the dose determination phase of the study)
5. Test subjects must have no known sensitivity to insect repellents or skin care products.
6. Test subjects must be attractive to stable flies, as evidenced by previously being bitten by stable flies (optional for dose determination)
7. Test subjects must not smoke or drink alcoholic beverages 12 hours prior to the test.
8. Test subjects must not use perfumed cosmetics, skin creams, shaving lotions, etc. after 8 P.M. the night before the test, and during the test.

ICR complies with the EPA's Final Rule governing the use of human test subjects, and adheres to 40 C.F.R. Part 26 Subparts K and L when it uses human subjects in studies.

**f) Institutional Review Board**

All EIRB documents will be submitted to EPA/HSRB as a package separate from the protocol. ICR uses the following institutional review board ("IRB"):
Essex Institutional Review Board, Inc. ("EIRB")
121 Main Street
Lebanon, NJ 08833

This IRB is accredited by PHRP (Partnership for Human Research Protection Inc.), and is currently in the process of obtaining accreditation from AAHRPP (Association for the Accreditation of Human Research Protection Programs).

Approval of all documentation for human subject testing must be obtained from EIRB, EPA, and the HSRB before such testing can occur.

**g) ICR's Use of Selection Criteria**

ICR has developed a pool of male and female test subjects. The test subjects ICR recruits represent a diverse group including retired teachers, business owners, contractors, engineers, as well as students, homemakers and others.

ICR will exclude pregnant and breast feeding women from this study due to ethical concerns. ICR will also exclude children under the age of 18 for the same reason. Individuals unable to read, speak, or understand English will be excluded to ensure that all test subjects understand the ICD and test parameters. Employees or relatives of employees of either ICR, the sponsor, or other interested parties, will be excluded to avoid the possibility of coercion. Individuals sensitive to stable fly bites, insect repellents, or skin care products will be excluded to avoid placing them at risk. Although these groups of people that ICR would exclude are groups of people who would probably use repellents, their exclusion is justified because this will protect them from potential hazard.

ICR's list of potential test subjects is as representative of potential repellent users as ICR is able to make it in terms of both practical and ethical considerations. ICR test subjects need to be in good health to withstand the rigors of the specific test. In the case of this laboratory test, the rigors will be very minor – boredom is likely to the main one. ICR will accept individuals between the ages of 18 and 70. This age group represents a large portion of the US population who would encounter stable flies and have a need to use insect repellents. Since there is no risk of arthropod-borne disease, exclusion of individuals over 55 is not justified.

ICR will select individuals from its database of candidate test subjects. This will be accomplished by drawing numbers that correspond to the candidate subjects. ICR will attempt to select even numbers of male and female test subject (6 female and 6 male in this test) to

eliminate any gender bias in this test. The reason for this is that gender has been shown to affect attractiveness of the subjects to mosquitoes and the same may be true of stable flies.

**h) Consenting**

All candidates will review and sign an Informed Consent Document ("ICD") prior to acceptance as study subjects. The ICD will be formally explained to all candidates before the study is scheduled to begin. A candidate may visit ICR to review and sign the ICD or the ICD can be mailed to the candidate for their review. If mailed, the study director will phone the candidate to answer any questions regarding the ICD. If any candidate refuses to sign after learning the details of the document, they will not be allowed to participate in the study. After the ICD is fully described to the candidate, he or she may then sign the ICD in the presence of an ICR staff and a copy of the ICD will be made and returned to the candidate. He or she will then be notified within one week if they have been enrolled as a subject in the study. The Informed Consent Document will have been approved by an Institutional Review Board before it is presented to the candidates for the study.

**i) Remuneration**

For the dose determination part of the study, the subjects will be paid $11/hour for a 9 hour day even though the duration of this part of the study is likely to be less than 4 hours per subject.

For the repellent part of the study, the subjects will be paid $11/hour for the first 9 hours and $17.50 for each additional hour they spend on the day of the study. The study will last about 10 hours with approximately one hour of preparation time for a total of 11 hours. A total payment of $134 will be paid to each test subject for the day. If a subject drops out of the test at our request but they have complied with all of our requests, they will receive full payment. If the subject drops out of the test either at our request because they have not followed all of our directions, or they just choose to drop out, they will be compensated for their time up to that point at the rate of $11 per hour.

Payments will be mailed to the subjects on the 15$^{th}$ or 30$^{th}$ of the month.

**j) Recruitment Procedures**

ICR has been conducting repellent studies for over thirty years. During this time ICR has amassed a large list of potential subjects. Some of these subjects refer friends and colleagues to ICR. When a repellent study is planned, ICR will contact candidate subjects in its data base by telephone and briefly discuss the study. Any study specific inclusion/exclusion requirements will also be mentioned at this time.

ICR will use a recruitment script to recruit test subjects for this study,⊗ (Appendix VI).

If the candidate is interested and is available, the inclusion/exclusion criteria will be discussed in more detail to determine if they qualify to participate. The ICD will also be discussed with them at this time. In addition, ICR will mail a copy of the ICD to each candidate for their review. They will be instructed to contact the study director to verify receipt of the ICD and to ask any ICD or study-related questions they may have.

The study director will contact all candidate subjects by phone several days after their receipt of the ICD to make sure that all their questions have been answered. All candidates will be offered the opportunity to come to ICR to go through the consent process in person. If contacted individuals choose to visit ICR office, they may voluntarily sign the ICD if they wish to be enrolled in the study. If they choose not to visit ICR's office prior to the study date, they must sign the ICD on the study day before taking part in the study.

Any candidate who declines to sign the ICD will not be permitted to participate in the study.

There will be no coercion for any candidate to participate. The inclusion/exclusion criteria are clear, the payment is simple; the candidates will be informed of the conditions they will likely encounter and what is expected of them.

Each female candidate will be informed that if they sign the ICD and want to participate in the test, they will be required to perform an over the counter pregnancy test on the morning of the study. The test results will be confirmed by a female ICR employee and the study director. Once they have signed the ICD, each consenting test subject will be informed that they may drop out of the study at any time without penalty (except that they will lose some of their potential remuneration, based on the time they miss). Further, they may leave as soon as practical after early withdrawal from the test.

**k) Pregnancy Testing**

After signing the ICD and shortly before any treatment with a test articles, each female candidate will take a pregnancy test as described by the label of an over-the-counter pregnancy test kit supplied by ICR. This will apply to the dose determination phase (section 11 below) and to the repellent test phase (section 20 below). Any subject who shows a positive result will be discretely excluded from further participation. The presence of multiple female subjects will allow the reason for their exclusion to be kept private. A female ICR staff member will confirm the pregnancy test results. The study director will be advised of the results, but no one else will be. The reason for the positive subject's exclusion from the study will be kept private by the study director informing the other subjects that this subject has not been able to meet one of the inclusion or exclusion criteria, without specifying which one.

## 11. DOSE DETERMINATION

### a) Introduction

The label directions on insect repellents provide general instructions on how much product to apply, but consumers may ignore these instructions or the instructions may be too vague to instruct the consumer adequately. The proposed study will include a dose determination phase before the repellent test is conducted. This will allow the products to be tested at rates which consumers are likely to use. Therefore 12 subjects will be recruited, as described above, to determine typical consumer doses for both products.

### b) Preparation of Subjects

ICR staff will measure the subjects' forearms and demarcate 250 $cm^2$ areas for treatment, as described subsequently, under *Personnel Preparation.*

### c) Separation of Subjects

It is important that subjects are not able to observe or converse with each other before or during application of the products as this could bias them as to how much they would apply. Therefore each subject will move to a separate room with an ICR staff member present before treatments begin.

### d) Applications of Cream Product

The subjects will be given a copy of the label for the cream product and a sample of the cream. They will be asked to apply the cream, according to label directions, to their forearm, using their gloved hand, until they have applied what, in their opinion, is enough. The weight of product applied will be calculated by weighing the product container before and after application. Subjects will then wash off the cream using soap and hot water, dry their arms and repeat the process for a total of three applications.

### e) Applications of Spray Product

The subjects will then be given a copy of the label for the spray product and a sample of the product itself. They will treat their forearms with the spray. They need to be able feel the spray hitting their skin in order to decide when enough has been applied, but some of the spray droplets will blow by their forearms, making accurate measurement of the dose applied difficult. Therefore a different method is called for. An approximately 5 cm wide band of water proof surgical dressing will be wrapped around the central part of each forearm with the impervious layer against the skin and secured by two rubber bands. A layer of gauze, or other absorbent material, will be wrapped around the dressing to provide additional absorbent capacity. The subjects will then spray their forearms until satisfied that enough has been applied. The dressing, gauze and rubber bands will be weighed before and after to determine the weight applied per unit area and converted to the weight to be applied per 250 $cm^2$. This procedure will be repeated for a total of three applications.

**f) Calculation of Dose**

The weights of the cream and the spray product will be averaged per subjects (mean of three applications per product). Then an overall mean will be calculated for all subjects for each product. These overall means will be the doses to be used in the repellent test with stable flies. The standard deviation and standard error of the mean will be calculated for each product across all subjects to determine the spread of application rates in this small sample of the general population.

## 12. NEGATIVE CONTROL

One subject will be selected to be the negative control. Selection will be by a drawing of numbers. One untreated arm of the control subject will be used to establish the aggressiveness of each cage of 25 stable flies.

Twenty five stable flies will be added to each cage at the start of test. The control subject will insert his/her untreated forearm into each cage and leave it there until two stable fly landings have occurred. An ICR staffer will gently push landing flies off the control subject's arm before they can bite by reaching in with a protected hand from a port on the other side of the cage with a wooden applicator stick. This approach will be needed since stable flies, unlike mosquitoes, can cling too tightly to a subject's arm to be easily shaken off. ICR staff will record the time when two landings occur.

If fewer than two stable flies land in 60 seconds in any of the six test cages, all stable flies will be vacuumed from all six cages and a new group of twenty-five stable flies will be released into all six cages.

No comparison will be made between the control landing rate and the treated subjects.

## 13. RATIONALE FOR NOT HAVING POSITIVE CONTROLS

Firstly, EPA is not requiring positive controls. Secondly, sufficient biting pressure (as evidenced by at least two landings in 60 seconds in a 250 $cm^2$ area on an exposed untreated control arm) will be confirmed at the start and throughout the study before each exposure period. Thirdly, a positive control group would not confirm the stable fly repellency of the test product nor would it help in determining a reliable protection period for these products under laboratory conditions. Finally, putting additional subjects at risk, however minimal, would be unethical.

## 14. SUPPORT STAFF

Additional ICR staff members will support the study director and test subjects in their activities These ICR staff members, along with the study director, will record all test data. Test subjects will not record any data. ICR staff are trained in the procedures to be used in this test and are familiar with ICR's SOPs. The quality of the study results could suffer and these results would be difficult to defend in one of the routine an EPA audits which ICR is subject to. The same difficulty would apply to a court of law if untrained test subjects recorded data.

## 15. MISCELLANEOUS SUPPLIES

Syringe, (minus the needle), micropipette and tips, Q-tip®s, latex or vinyl gloves, clip boards, data record forms, scissors, elastic bandages, water proof surgical dressing, gauze, rubber bands, Elastikon® tape, pencils, marking pens (e.g. Sharpie®), hygrothermograph, unscented Neutrogena® soap, paper towels and a stop watch, Caladryl® or Calamine® lotion.

## 16. RECORDS TO BE MAINTAINED

All study notes, data collection sheets (true copies), SOPs (originals), Chain of Custody letters (true copies), Sample Log and Sample Record of Use Forms (true copies), the protocol (true copy) and signed Informed Consent documents will be maintained in the ICR archives. Original documents will be provided to the sponsor for archiving with the exception of SOPs, Master Schedules, signed Informed Consent documents, test article characterization, and personnel files.

## 17. RISK CHARACTERIZATION AND MINIMIZATION

The subjects will be exposed to two types of risk:

1. *Test products.*

These proposed insect repellents use the active ingredient, Picaridin, which was registered by the US EPA under FIFRA on December 7, 2000. As required under FIFRA, registration of Picaridin is supported by an extensive data package that includes toxicity test data that demonstrate low acute and chronic toxicity. The EPA "New Pesticide Fact Sheet" for Picaridin indicates that its toxicology data base is complete and no additional studies are required. This active ingredient has been used without significant incident by the study sponsor and other insect repellent companies and many consumers. All of the inert ingredients used in the finished insect repellent products have a long history of safe use in various cosmetics.

For registered products containing Picaridin®, the EPA risk assessment assumes that each application of insect repellent products is to a skin surface area of 4,538 $cm^2$ for adults. In the proposed test, the product will be applied once to the subjects on the test day over a surface area of only 500 $cm^2$ (*i.e.* 250 $cm^2$ on each forearm). Consequently, the test subjects in this study will only be exposed over an area of approximately 11 percent of that previously reviewed and approved by EPA for products with the same Picaridin® concentration. Further, the label directions of these registered products allow for up to two applications per day, while the efficacy study will employ only one (however the dose determination study will involve three or occasionally, four applications). A minimum 100-fold margin of exposure (MOE) is considered to be the target for the determination of acceptable risk from systemic exposure. The MOE is based on the No Observed Adverse Effect Level (NOAEL) for systemic effects, the concentration of active ingredient in the formulation, frequency and rate of application, skin surface area and body weight, and dermal absorption. The MOE for the test subjects in this efficacy study will substantially exceed the minimum 100-fold target and is, therefore, considered acceptable under widely recognized scientific standards.

While there is little concern for the test articles to induce an adverse reaction in the test subjects, they will be monitored throughout the study and prompt medical attention will be obtained if any adverse reaction is observed among the subjects in the test. Those individuals who are known to have allergies to stable fly bites, insect repellents, or skin care products will be excluded from the study.

2. *Bites from stable flies.*

The principal effect of a stable fly bite is a sharp but transient pain. In most cases, stable fly bites do not lead to the itching and localized swelling which are the typical aftermath of mosquito bites. A few people may experience a small area of redness, swelling and itching that usually goes away within 24 hours. In extremely rare cases, a serious reaction to a bite may result in swelling of the throat, hives and wheezing. This condition (anaphylaxis) could be life-threatening and requires immediate medical attention. All subjects known to have severe reactions to stable fly bites will be excluded from this study.

All subjects will wear latex or vinyl gloves. Only a small portion (250 $cm^{2)}$ of bare skin on each arm will be exposed. All other parts of the body will be covered with the subject's personal clothing. This will protect them in case of any escaped flies. Immediately upon receiving a FCB on an arm, that arm will be withdrawn from the test and not be exposed to the caged stable flies again. Caladryl® or Calamine® lotion and rubbing alcohol will be available for use to mitigate any reaction to stable fly bites.

An ICR staffer trained in First Aid will be on site, and First Aid supplies will be available. A selected local hospital will receive prior notification of this study and on-site staff will have cell phones to make emergency calls if necessary. In the case of medical emergency, people will be

transported to the selected local hospital, St. Agnes Hospital, by either ICR staff or ambulance. The hospital is 7 miles from ICR, at 900 S. Caton Ave., Baltimore, MD. 21229. The telephone number of the ER center is 410-368-2000. If any test subjects need medical attention, their medical care will be paid by ICR.

*Arthropod-borne diseases*

As noted previously, there will be no risk for arthropod-borne diseases from the stable flies used in this study. Stable flies are known to carry human diseases only very rarely, if at all. More importantly, this strain has been reared in the laboratory for many years and has not been allowed to feed on human blood (bovine blood is used). Owing to the forgoing factors, transmission of a blood-borne disease by these stable flies is not possible.

Finally, the subjects will only need to receive two bites within 30 minutes to confirm breakdown, after which the test arm will not be exposed to flies again, thus minimizing their exposure to the flies.

## 18. DISCOMFORT AND HAZARD

The stable flies being used in this test are not capable of transmitting diseases in the wild. This strain of stable fly has been laboratory colonized for many years and has not been exposed to outside blood sources while at ICR. None of the stable flies used in this test will have had a blood meal prior to their introduction into the test cages. Once a group of stable flies has been used in a study, it will not be re-used in another study. All stable flies used in the study will be destroyed either through freezing or carbon dioxide. Transmission of a blood-borne disease by this strain of stable fly is not possible.

In the event that study related injury or illness should occur, test subjects would be instructed to seek medical attention through a health care provider, at ICR's expense. Test subjects would be instructed to submit study related bills to ICR for payment. ICR will incur the cost of any such study-related bills. The study director will contact all test subjects by telephone, two weeks after the conclusion of the study, to inquire if they have experienced any adverse effects.

## 19. BENEFITS

The sponsor will gain the most benefit from this study through knowledge gained on the performance of its repellent products. Indirect benefit may accrue to society at large by the development of more effective, safer and 'pleasant-to-use' repellent products, and alternatives to DEET-based products.

## 20. REPELLENT TEST METHODS

**a) Experimental Design**

The purpose of this study is to determine the extent to which a stable fly repellent is effective in preventing bites on exposed human skin. The repellent will be considered degraded if either of these two conditions is met: a) two stable fly bites are noticed in a single 5 minute observation period; or, b) a single bite in two adjacent observation periods is noted. The goal of the study is to provide an estimated length of protection time that a specific repellent provides.

Individuals will have repellent applied to a specific area of their forearms. Then, their arms will be exposed to live stable flies for five minutes. If two bites are noted in this time period, the case will be considered a "bite". If no bites are noted, the arm will be removed and re-exposed 30 minutes later for another 5 minutes. This process will continue either until two bites are noted or 10 hours have elapsed. The 250 $cm^2$ delineated areas on the arms of subjects will be treated and used as test areas. Only arms are being treated in this study, since arms are easy to monitor for stable fly activity. Therefore there will be twelve test arms for each treatment. Each test subject will have one arm treated with the cream product and the other arm will be treated with the spray product. ICR staff will know the identity of the treatments, but the test subject will not.

**b) Rationale for Sample Size : Number of Subjects**

The EPA draft Guideline OPPTS 810.3700) currently (1/2008) on EPA's website recommends 10 test subjects to document a protection time greater than 5 hours. Because of the high cost of doing repellent studies and the need to avoid unnecessary exposure to subjects, it is prudent to ensure data is collected from the minimum acceptable number of subjects. Therefore the target number of test subjects in the study is twelve, which includes two additional subjects in case of drop outs or ones failing to meet an exclusion or inclusion criterion on the day of the test. There will also be one negative control subject.

The choice of 12 subjects is discussed further in DATA ANALYSIS (section 23).

**c) Test location:**

This test will be conducted in the laboratory at ICR. The laboratory is maintained at ambient relative humidity and 70° F ± 15°F. These are the same conditions as the stable flies are reared under so their activity should be unimpaired; there is no need for elevated humidity as is the case with mosquitoes.

**d) Dose**

The dose will have been determined from the dose determination part of the study conducted prior to the beginning of the repellent test (see *Dose Determination* above). This dose must be

no greater than 4 mg/cm$^2$. If it is greater, an additional approval will be needed from EIRB before the repellent test can take place, since 4 mg/cm$^2$ has been given to ERIB as the upper limit for their evaluation.

**e) Blinding of the Study**

The test articles will be coded as "A" (cream) and "B" (spray). During the test these codes will be the only test article designation referred to or that the test subjects will see. The study director and members of the ICR staff will know the actual test articles, but will refrain from such identifications in the presence of test subjects. It should be noted however that the different appearance and texture of the cream and the spray will probably be apparent to the subjects.

**f) Treatment Groups and Subject Selection**

There will be two groups: a treated group of twelve (two more than required to allow for drop outs) subjects whose arms will be treated, and one untreated (control) subject whose arms will be untreated. Subjects will be given a subject number. They will be assigned to the groups by lottery selection of the subject number.

**g) Personnel preparation**

All subjects will have reviewed and signed an ICD before acceptance as a test subject participant.

i) *Pregnancy Testing*

All female subjects will conduct a urine pregnancy test on the morning of the test before any treatments. This procedure was described under section 10k.

All test subjects will then wash their arms with unscented Neutrogena® soap. The test subject's arms will then be measured in the following manner for the demarcation of the 250 cm$^2$test area:

*ii) Measurement of 250$^2$ cm areas*

The determination of the 250 cm$^2$ area of each subjects' forearms is based on the assumption that they approximate a truncated cone shape. The subject's elbow will be placed on a tabletop with the forearm held perpendicular to that surface. A mark will be made on the upper forearm 3 inches from the tabletop. A second mark will be made on the lower forearm at a point just below the wrist bone. The circumference of the arm will be measured at each of these points. The average of the two circumferences will be calculated. This represents the approximate circumference at the center point between the two marks. A third mark will be made at the center point between the two marks. The average circumference will be divided into 250cm$^2$, the total exposed surface area required for the test. This will yield the length of arm required to be exposed. The end points of this length of exposure area will be marked on the forearm so that each end point is equidistant from the center point. The endpoint measurements from the center point will be recorded so that they may be duplicated in the test. The distance from the tip of the

little finger to the center point will be measured and also recorded so that the center point may be duplicated at another time.

The above mentioned measurements will be recorded on a repellent measurement form. If a test subject has been previously measured, the existing measurements will be used.

iii) *Delineation of 250$^2$ cm areas*

The test subjects and the control subject will have 250 cm$^2$ areas delineated around their forearms and these arms will be prepared for treatment. The skin above and below the target area will be protected with elastic bandages and or Velcro® straps held in place with Elastikon® tape. Arms will be protected by shirt sleeves. Latex or vinyl gloves will be given to the subjects to protect their hands.

*iv) Determination of Attractancy to Stable Flies*

Test subjects will be checked for their attractiveness to stable flies. Subjects will place their right forearm into their cage and the number of flies landing on their arms will be counted. The required landings will be at least 2 stable flies in 60 seconds to qualify a subject as being attractive to the flies. Volunteer will repeat the qualifying exposure as above using the left arm. The procedure will be repeated if the subject fails to qualify. If a subject again fails to qualify after repeated exposures, that subject may be dropped from the study.

After qualification the test subjects will be treated with the two repellent products.

*v) Treatment*

The repellents will be coded as "A" (cream) or "B" (spray), and each arm will be labeled on the protective wrap with the code corresponding to the repellent applied. Each test subject will be treated on the right arm with repellent "A" and on their left arm with repellent "B".

The test articles will be applied to the test subjects using a syringe (minus needle), rubbed on by hand by an ICR staffer using their surgically-gloved hands. If the cream repellent is too viscous to be applied with a syringe, it will be applied with a cotton-tipped applicator stick. The amount of test article applied will be determined in the dose range finding. The hands will be protected with gloves. The control subject will receive no treatment. In the case of the spray, the product will be dispensed into a 250 ml beaker after which it will be applied by syringe (minus needle). Application of the spray will differ from the manner in which it will be used by consumers or in the dose determination phase of the study. Application by syringe is, however, required to allow accurate measurement for equal treatment.

Subjects will be treated in pairs. Both members of a pair will be treated with the cream and then with the spray. The time of treatment will be the time when the application of the spray treatment

begins. This time will represent the starting time used for calculation of the protection times afforded by the test articles.

**h) Testing**

A group of 25 stable flies will be placed in each test cage prior to the first exposure period. The aggressiveness of the caged stable flies prior to each exposure period will be determined from the landing rate on the control's arm before each test exposure. Once the landing rate has been confirmed (at least 2 landings in 60 seconds), the counts will cease. The landing rate verification will be conducted before each exposure of the treated test subjects. If fewer than the required number of stable flies land in 60 seconds, a new group of 25 stable flies will be released into that cage (as well as into the other 5 cages so as to avoid bias) after the old flies have been removed with a vacuum.

ICR staff will assist the test subjects in inserting their arms into the test cages, taking care not to rub them on the cloth sleeve. The test subjects will expose their treated forearms to the stable flies for 5 minutes. The subjects will then remove their arms from the cages with assistance from an ICR staff. Exposures to the stable flies will be repeated every 30 minutes until the treatment on any given forearm is determined to be no longer effective or until 10 hours have elapsed, whichever occurs first.

The test data to be recorded will be bites. Test data will be recorded on a Repellency Test Data Sheet.

**i) Rationale for using Bites instead of Landings as the End Point**

Bites will be used as the end point instead of landings in this test for the following reasons.

i). A fly which has been allowed to bite after it lands (takes blood into its abdomen) is less likely to land again than a fly which was brushed away after its first landing before it could bite to take blood. This fly will probably land again so it can get the blood meal it needs. This one fly could thus account for both the first landing and the second (confirming) landing. Aspirating stable flies once they land will frequently not be successful since they are elusive flyers and cannot always be captured on the first attempt by aspiration once they have landed (this was tried at ICR during protocol development). In such cases, the fly which landed cannot be identified from among the other 24 flies in the cage for subsequent attempts at aspiration. Once a stable fly has bitten and fed, however, it is much less likely to bite again as it will have accomplished its goal of securing a blood meal. Using bites therefore will greatly increase the chances that two different flies will be involved in the determination that the repellent product has lost its repellency (broken down).

ii). Unlike field testing of mosquitoes, where there is the possibility of a bite transmitting a disease, these lab-reared stable flies do not carry disease.

iii). The bite of a stable fly usually results on in transient pain only, without the ensuing itching and welting associated with mosquito bites.

iv). Stable flies in the wild usually land on one's ankles and lower legs. Therefore, if they only land and do not bite, one may not even notice them. It is only when they bite that they become a nuisance. It is more important therefore to demonstrate that the repellent prevents bites rather than landings.

v). Stable flies often land long before they bite. A conservative analysis of 9 stable fly tests conducted by ICR from 1990 to 1999 revealed that the time difference between first confirmed landing and first confirmed bite ranged from 0 to 7.5 hours with a mean of 2.6 hours. Therefore ladings would seriously underestimate the protection time for the test products.

**j. Criteria for Test End Point**

The test subjects will continue to expose their treated arms to stable flies until the FCB (First Confirmed bite) or until 10 hours have elapsed, whichever occurs first. The FCB occurs when two bites occur on the same arm in the same exposure period, or one bite occurs in each of two consecutive exposure periods (the first bite being the confirmed bite). A bite is defined as a stable fly penetrating the skin with its proboscis and taking blood into its abdomen. When the two bites have occurred as noted above, the test will terminate on that arm.
The test will be terminated on each treated arm after an FCB occurs. The subject will then be able to remove the bandages and tape, scratch and wash that arm. If they want to, they can use rubbing alcohol to help stop any itching from bites they have received. Caladryl® or Calamine® lotion may also be used. When the testing is terminated for the first arm, the subject will roll down their sleeve on that arm.

If a single bite occurs without a confirming second one within that exposure or the following one, that bite will not count towards product breakdown – two additional bites, within one or two consecutive exposures, will be required.

## 21. CONFIDENTIALITY

The information obtained from test subjects taking part in this test may be used by ICR and its sponsor and may become part of a report. This report will be kept as confidential as possible under local, state and federal law. The test subjects' first and last initial and their dedicated identity number only may be referenced. ICR cannot guarantee that the subjects' identity will be kept confidential. Essex Institutional Review Board has the right to review the subjects' records.

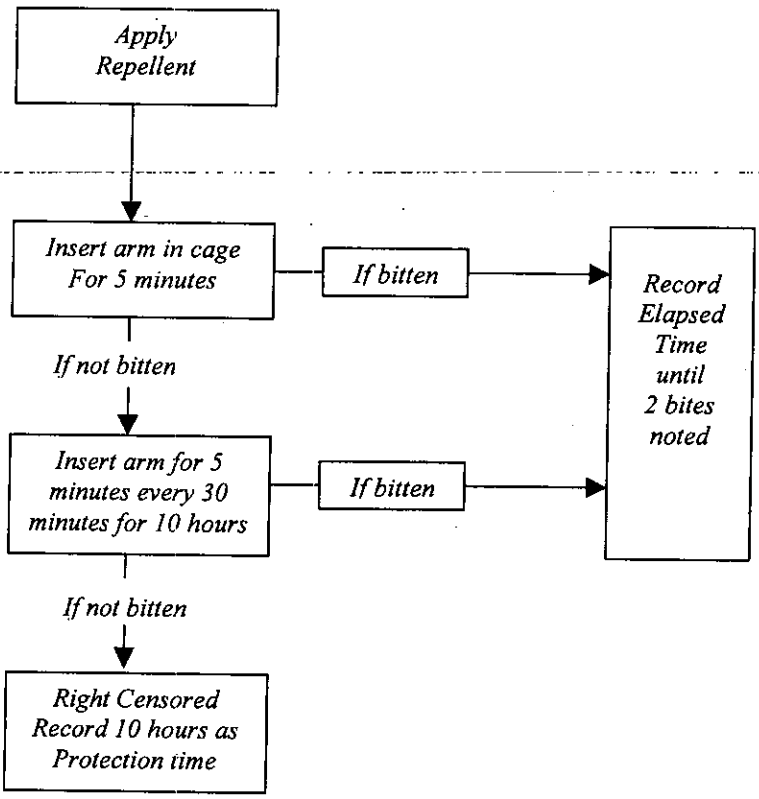
## 22. DATA ANALYSIS

**a) Goals**

The purpose of this study is to determine the extent to which a stable fly repellent is effective in preventing bites on exposed human skin. The repellent will be considered degraded if either of these two conditions is met: a) two stable fly bites are noticed in a single 5 minute observation period; or, b) a single bite in two adjacent observation periods is noted. The goal of the study is to provide an estimated length of protection time from a first confirmed bite (FCB) that a specific repellent provides.

**b) Methodology**

Individuals will have repellent applied to a specific area of their forearms. Then, their arms will be exposed to live stable flies for five minutes. If two bites are noted in this time period, the case will be considered a "bite". If no bites are noted, the arm will be removed and re-exposed 30 minutes later for another 5 minutes. This process will continue either until two bites are noted or 10 hours have elapsed. The methodology is graphically presented below:




Subjects will be assessed for product efficacy every 30 minutes over the 10 hour study interval. Thus for each complete subject, there will be 20 assessments of protection efficacy (2 assessments per hour X 10 hours).

**c) Statistical Procedures:**

***Power.*** Based on a meta-analysis of mosquito studies of this type, Rutledge and Gupta (1999) provided power tables for determining the number of subjects needed to determine protection times up to 8 hours with varying confidence limits and two-tail levels of significance. Using information from their study, 11 subjects would be necessary in order to have a 95 % confidence interval for assessing protection up to 8 hours with a ± 2-hour confidence limit.

The proposed study will use stable flies as the test organism, not mosquitoes. Stable fly behavior differs from that of mosquitoes, a meta-analysis for the former species is needed for a confident prediction of the sample size needed for a reliable estimate of protection time. ICR is unaware of

any such study. We analyzed our own database consisting of 9 stable fly repellent studies conducted between 1900 and 1999 in which the numbers of subjects ranged from 2 to 10. Our consulting statistician is of the opinion that the data are inadequate for deriving a reliable power estimate table, especially as many of the protection times were left (<0.5 hours) or right (>8 hours) censored. When these data had been excluded, the remaining data did not show survival time being significantly linked to standard deviation. With these caveats and following the procedures outlined by Rutledge and Gupta (1999), he derived the table shown below for 95% confidence levels, two-tailed with a 2-hour confidence interval.

| Time (in hours) | Standard Deviation | Sample Size |
|---|---|---|
| 1 | .95 | 1 |
| 2 | 1.18 | 2 |
| 3 | 1.42 | 2 |
| 4 | 1.65 | 3 |
| 5 | 1.89 | 4 |
| 6 | 2.12 | 5 |
| 7 | 2.35 | 6 |
| 8 | 2.59 | 7 |

The table indicates that a sample size of seven subjects would be adequate. In view of the uncertainties noted above relating to this table, we have chosen to run this study with twelve subjects in an effort the minimize the risk of interpreting repellent protection from a too small data set.

**d) Analyses.**

Data will be analyzed using SPSS v. 16 software. The Kaplan-Meier (KM) product-limit technique will be used to describe and analyze the length of time to product degradation. KM allows for the presence of right censored data and provides survival proportions as well as mean survival times with corresponding confidence intervals accordingly. Because the KM procedure is based on proportions, there is no need for the underlying scores to be normally distributed. From the KM analysis we will take the mean and median survival times along with its 95% confidence interval as the final result of this study.

In the event that *all* subjects right censor (i.e., last the entire 10 hours without any bites), we will conclude, with 95% confidence, that the product can provide protection for up to 8 hours, ± 2 hours.

In the event that *more* than two subjects drop out during the study, final estimates of protection time will be made that are consistent with the power parameters stated above.

## 23. QAU AND DATA ARCHIVING

Good Laboratory Practices, as outlined in 40 CFR §160 will be followed throughout the study. The QAU representative will observe and write phase report(s) for this study. All data will be archived.

## 24. SCHEDULE OF EVENTS

| DATE | PROCEDURE |
|---|---|
| Time Zero | Test Conducted |
| At End of Test | Verbal Report |
| After The Laboratory Test Conduct | Written Report |
| After Final Report Has Been Issued | Test articles Returned |

## 25. STATEMENT OF AMENDMENT OR DEVIATION

Any amendments to this protocol must be discussed with and approved by the Sponsor. Any amendments to, or deviations from, this protocol will be documented in the final report.

Robin G. Todd PhD, BCE
Director, ICR, Inc. 2/4/08 Date

Ellen W. Quinn
QAU, ICR Inc. 2/4/08 Date

William J. Gaynor
Study Director, ICR Inc. 2/4/08 Date

G.K. Sangha PhD
Representative
LANXESS Corporation 2-1-08 Date

**APPENDIX I:**
**DATA COLLECTION SHEETS**

**RAW DATA COLLECTION SHEET**

SPONSOR: 433 DATE: TIME:
S D/TECH: William J. Gaynor SPECIES: S. *calcitrans*

PRE-TEST LANDING RATES

SUBJECT Initial and Number:

| TIME (SECONDS) REQUIRED FOR 2 LANDINGS | |
|---|---|
| RIGHT FOREARM | LEFT FOREARM |
| | |
| | |
| | |
| | |
| | |

Signatures of Study Associates Recording data on this sheet/date: .....
Study Director's Signature/Date .....
Test Subject's Initials/Date .....

**RAW DATA COLLECTION SHEET**

SPONSOR: 433 DATE: START TIME:
S D/TECH: William J. Gaynor SPECIES: S. *calcitrans* TEST ARTICLE APPLIED BY:

| TEST ARTCL | SUBJ ECT NUMBER: | | SUBJ ECT NUMBER: | | CONTROL SUBJECT No. :_____ |
|---|---|---|---|---|---|
| | | | | | TIME FOR 2 LANDINGS (seconds) |
| TIME (Hours) | RIGHT ARM | LEFT ARM | RIGHT ARM | LEFT ARM | |
| | BITE | BITE | BITE | BITE | |
| 0.5 | | | | | |
| 1.0 | | | | | |
| 1.5 | | | | | |
| 2.0 | | | | | |
| 2.5 | | | | | |
| 3.0 | | | | | |
| 3.5 | | | | | |
| 4.0 | | | | | |
| 4.5 | | | | | |
| 5.0 | | | | | |
| 5.5 | | | | | |
| 6.0 | | | | | |
| 6.5 | | | | | |
| 7.0 | | | | | |
| 7.5 | | | | | |
| 8.0 | | | | | |
| 8.5 | | | | | |
| 9.0 | | | | | |
| 9.5 | | | | | |
| 10.0 | | | | | |
| FAIL | | | | | |

Signatures of Study Associates recording data: .....Study Director's Signature/Date .....
Test Subject's Initials/Date _____

# Repellent Measurements–Arm

SUBJECT:

DATE:

**LEFT ARM**

LOWER ARM =

AVG = 250 cm = =
2

UPPER ARM =

CENTER POINT = DISTANCE FROM LARGE TO SMALL CIRCUMFERENCE ____cm.= 2

DISTANCE FROM CENTER POINT TO TIP OF LITTLE FINGER

DISTANCE FROM EITHER SIDE OF CENTER POINT

**RIGHT ARM**

LOWER ARM =

AVG = 250 cm = =
2

UPPER ARM =

CENTER POINT = DISTANCE FROM LARGE TO SMALL CIRCUMFERENCE ____cm. = 2

DISTANCE FROM CENTER POINT TO TIP OF LITTLE FINGER

DISTANCE FROM EITHER SIDE OF CENTER POINT

DATA TRANSFER VERIFIED BY:_____DATE:

## APPENDIX II:
## INFORMED CONSENT DOCUMENT – DOSE DETERMINATION

Test subject's initials:.....

Date:.....

**PROTOCOL:** EVALUATION OF THE EFFICACY OF KBR 3023 (PICARIDIN; ICARIDIN) – BASED PERSONAL INSECT REPELLENTS (20% CREAM, 20% SPRAY) AGAINST STABLE FLIES IN THE LABORATORY

## INFORMED CONSENT AUTHORIZATION TO PARTICIPATE IN THE DOSE DETERMINATION PHASE OF AN ICR, INC. STABLE FLY REPELLENT EVALUATION IN THE LABORATORY

**Principal Investigator: William J. Gaynor**
**Address: ICR, Inc. 1330 Dillon Heights Ave. Baltimore, MD**
**Telephone Number: 410-747-4500**
**24 Hour Emergency Number: 410-207-0415**

**Purpose of Study**

We (ICR, Inc.) have been contracted by LANXESS Corporation to conduct a research study in our laboratory on two insect repellent products containing the active ingredient picaridin, to find out how well these products repel stable flies. Before this study can be performed the dose of the two repellents to be used in the study must be determined based on how much product a typical consumer would apply to themselves. This dose determination phase of the study is the study for which we are asking you for your participation. This dose determination phase of the study will occur in the ICR, Inc. lab where the stable fly repellents will later be tested using the doses you determine today. We have prepared this Informed Consent Document (ICD) to explain this dose determination study to you so that you can make a free choice whether or not to participate.

We will review this document with you to make sure you understand what would be expected of you if you participate, and to explain the risks you would face through your participation. Please ask us about anything you do not understand. If you have come into our office to review the document, you may take it home with you if you need more time to think about whether to participate.

We will apply the eligibility standard listed below to determine if you qualify to participate in the study. If you qualify, we will ask you to consider signing this document to indicate your consent to participate. Your signing indicates your willingness to participate in this study, but you would still be free to withdraw from the study at any time, without having to give a reason.

Test subject's initials:.....

Date:.....

If you decide you would like to participate, initial each page of this form and sign the last page in the presence of the ICR staff. The Principal Investigator will sign the form as well, and you will be given a copy with both signatures. We will notify you by phone within one week whether you have been selected for the study.

**Eligibility for the Study**

To participate in this study you must meet the following conditions:

- Sex: Six of each: Male and Female
- Age: You must be at least 18 and not over 70
- Race: No exclusions
- Literacy: You must be able to read, speak, and understand English
- You must not be pregnant or breastfeeding. If you are female, you will be required to perform an over-the-counter urine pregnancy test on the morning of the study. ICR will provide the test kit, and a female ICR staff member will verify the results. ICR will keep the results of the pregnancy test confidential from everyone except you and the Principal Investigator.
- You must not be an employee or a relative of an employee of ICR Inc., LANXESS Corporation, or any other party with an interest in this research.
- You must have no known sensitivity to insect bites/stings, repellents or to skin care products

If you choose to participate in this study and are selected to be a study subject, you must also agree:

- To follow the directions of the Principal Investigator and other ICR staff..
- Not to use tobacco, alcohol, or any scented cosmetic products after 8 p.m. the night before study, and on the day of the study until it is concluded.

Test subject's initials:.....

Date:.....

**Dose Determination Phase Summary**

Twelve subjects will participate in this one-day laboratory study. Each of you will apply the cream repellent and the spray repellent to your arms three times. You will apply as much as you normally would, without any instructions from us as to how much to apply. We will measure the amount of repellent you applied and average that amount with the amount the other participants applied to determine the dose to be used in the repellent study. This study will take less than 9 hours for all 12 test subjects. If you finish early, you will be allowed to leave earlier. The entire test will be conducted in a room maintained at comfortable temperature and humidity.

**Procedures**

On the day of the study, before the test begins:

- We will review this document with you and answer any additional questions you may have since you have signed it.
- You will wash your arms with unscented Neutrogena® soap.
- We will measure and mark a 3 to 5 inch wide test area around each of your forearms as described in detail below.
- You will apply the spray and cream repellents three times to the treated area of your forearms in the amount that you would normally apply.
- We will weigh the amount of repellents you and the other 11 test subjects applied and average them to determine a testing dose.

**Here is how that will work in detail**

**Laboratory Study Details**

1. All 12 of you will be involved in treating your forearms with each of the two repellent products. You must not observe or discuss with other subjects any of these procedures.

Test subject's initials:.....

Date:.....

2. We will measure the distance around your arm at the wrist and the elbow, and calculate how wide a band is needed for the standard test area on your arm. This 3 - 5 inch wide band will be wider on thinner arms; narrower on bigger arms. We will then use a felt-tip pen to mark the location of the band around each of your forearms.

3. We will cover the skin above and below the marked test area with multiple layers of elastic bandages and or Velcro® straps held in place with adhesive tape.

4. You will then put on a latex or vinyl glove and use a gloved finger to apply the cream repellent to the treatment area of your forearm until you feel you have applied the amount of repellent you would apply if you were applying it at home.

5. We will determine how much product you applied by weighing the repellent container before and after you use it.

6. You will apply the cream repellent a total of three times in the same way. Between applications you will wash your forearm with unscented Neutrogena soap until you feel that you have washed off all the repellent. You will then dry your arm with a paper towel and then let it air dry until your arm feels completely dry.

7. We will then measure the amount of the spray repellent you would typically apply. We will take an average of your three applications and of all the other subjects. Finally we will take an average of these 12 subject averages.

8. We will wrap a 2 inch wide strip of waterproof dressing around the middle of the test area on your arm (waterproof side against your skin). Then we will wrap a 2 inch wide band of surgical gauze around the dressing. We will secure the gauze and the dressing with two rubber bands. Your forearm will now have a band of dressing (with gauze on top) and bare skin on either side.

9. You will then spray the second repellent over the entire marked out treatment band area of your forearm (including the gauze-covered dressing) until the amount of product you have applied to the two bare skin areas of your forearm feels like what you would apply if you were using the product at home.

Test subject's initials:.....

Date:.....

10. We will remove the gauze-covered dressing and weigh it to calculate the amount of product you applied.

11. You will repeat this spraying process two more times, washing and drying your forearm as you did with the cream repellent between applications. We will use new bands of dressing and gauze for each of the three sprayings.

12. Once you have applied both the cream and repellents three times, your involvement in the test is done. You may remove your bandages, wash your forearms, and go home.

13. The day's study may last up to nine hours for all 12 test subjects, although your direct involvement should not last more than three hours. You may either bring your own lunch or pay to have lunch ordered.

**Discomfort and Hazard**

**Reaction to the test repellents:**

You may have a reaction to the test repellents.

The Sponsor has minimized this possibility by choosing an active ingredient (picaridin) that has demonstrated low oral, skin, and inhalation toxicity. The Environmental Protection Agency (EPA) has classified it as low toxicity for inhalation toxicity and primary skin irritation. EPA has classified the two test repellents as having low to mild toxicity based on eye irritation. For this reason it is important not to rub your eyes with your treated arms. The Sponsor has selected the non-repellent ingredients in the formulations because they are widely used in cosmetics and have a long history of safe use. ICR staff will be monitoring all subjects for any signs of a reaction to the test repellents. If you think you may be having such a reaction, tell a member of the staff immediately. A reaction may include redness, irritation, burning, swelling or a rash.

Should you have any medical problems, we will have First- Aid- qualified staff members, and supplies on site. We will have cell phones to make emergency calls if necessary. In the case of medical emergency, we will transport you to a selected local hospital at our expense. We will pay all of your medical bills for study-related illnesses and injuries. The Principal Investigator will

contact you by telephone, two weeks after the study to ask if you have experienced any adverse effects. You should contact the Principal Investigator any time after the study if you experience any study-related adverse effects, either before or after this follow up call.

**Financial Consideration**

We will pay you $11/hour for the 9 hour duration of the study for a total payment of $99. This payment will be mailed to you on the 15th or the last day of the month. If we ask you to drop out of the test, and you have complied with all of our requests, you will still receive full payment. If we ask you to drop out of the test because you have not followed all of our directions, or if you choose to drop out of the test, we will compensate you for time up to that point at the rate of $11 per hour.

**Costs**

There are no financial costs to you for participating in this study.

**Benefits**

You will get no personal benefit from participating in this study. The main benefit of this dose determination study is that it establishes the dose of the repellents to be tested in the subsequent stable fly repellent study.

Some benefit may result for society in general through showing the effectiveness of these products in repelling a noxious pest.

**Your Rights**

We will give you an opportunity to discuss with us any aspects of this document or of the study it describes that are not clear to you, so that you fully understand the nature of the study, its purpose, and the procedures to be used, as well as the discomforts, and risks you may experience during or after the study. You are encouraged to ask questions at any time, before or after you consent to participate, and before, during, or after the study day itself. Your participation is entirely voluntary. You may decide not to take part in this study, and if you decide you would like to participate, you

Test subject's initials:.....

Date:.....

are free to change your mind at any time without having to explain, and without penalty or loss of benefits to which you may be otherwise entitled.

**Alternative**

The only alternative is not to participate.

**New Information**

You will be informed verbally or in writing of any significant new findings discovered during the course of this study which may influence your continued participation.

**Voluntary Participation/Withdrawal**

You may be withdrawn from the study even if you want to continue. This could happen if (1) the study director believes it is in your best interest for you to stop being in the study, (2) or if you do not follow instructions for the study, (3) or if the sponsor stops the study for administrative or any other reasons.

**Questions**

If you have any questions about this study or suffer a reaction you think might be associated with the study, call us at 410-747-4500. If you have any questions about your rights as a research participant, or any related concerns or complaints, you may contact the Essex Institutional Review Board (IRB), 121 Main Street, Lebanon, NJ 08833, telephone 908-236-7735. The Essex IRB is a committee that has reviewed this research project to help ensure that the rights and welfare of the participants are protected and that the study is designed and carried out ethically. Review of this study by the Essex IRB is not an endorsement of the study or its outcome.

**Research Participation Information**

You can obtain information about participating in research studies from a number of sources.
A few are:

- Center for Information and Study on Clinical Research Participation (CISCRP): www.ciscrp.org
- Food and Drug Administration (FDA): www.fda.gov

Test subject's initials:.....

Date:.....

- Office for Human Research Protections (OHRP): www.hhs.gov/ohrp
- National Institute of Health: www.clinicaltrials.gov
- National Cancer Institute: www.nci.nih.gov
- Center Watch: www.centerwatch.com
- Various large university websites
- Various associations and societies concerned with specific diseases websites.

**Confidentiality**

We and the sponsor or its agents may use the information obtained from your taking part in this test, and this information may become part of a report. We will keep your participation as confidential as possible referring to you in the study data and reports only by your initials or an arbitrary ICR identification. However, we cannot guarantee that your identity will be kept confidential; the sponsor, personnel associated with the study, a regulatory agency such as the Environmental Protection Agency (EPA), and the Essex Institutional Review Board (EIRB) all have a right to review your records.

**Consent**

I voluntarily agree to participate in this study. I will be given a copy of this signed form.
By signing this form I have not given up any of my legal rights.

_____

Printed Name of Subject

_____

Signature of Subject Date

_____

Signature of Person Obtaining Consent Date

_____

Signature of Principal Investigator Date

Test subject's initials:.....

Date:.....

## APPENDIX III:
## INFORMED CONSENT DOCUMENT – REPELLENT TEST

Test subject's initials:.....

Date:.....

**PROTOCOL:** EVALUATION OF THE EFFICACY OF KBR 3023 (PICARIDIN; ICARIDIN) – BASED PERSONAL INSECT REPELLENTS (20% CREAM, 20% SPRAY) AGAINST STABLE FLIES IN THE LABORATORY

## INFORMED CONSENT AUTHORIZATION TO PARTICIPATE IN AN ICR, INC. STABLE FLY REPELLENT EVALUATION IN THE LABORATORY

**Principal Investigator: William J. Gaynor**
**Address: ICR, Inc. 1330 Dillon Heights Ave. Baltimore, MD**
**Telephone Number: 410-747-4500**
**24 Hour Emergency Number: 410-207-0415**

**Purpose of Study**

We (ICR, Inc.) have been contracted by LANXESS Corporation to conduct a research study in our laboratory on two insect repellent products containing the active ingredient picaridin, to find out how well these products repel stable flies. The stable flies used in this study are laboratory-reared and do not carry any diseases. This study will take place in the ICR, Inc. lab with stable flies confined in cages. This document will explain the study to you so that you can make a free choice whether or not to participate.

We will review this document with you to make sure you understand what would be expected of you if you participate, and to explain the risks you would face through your participation. Please ask us about anything you do not understand. If you have
have come into our office to review the document, you may take it home with you if you need more time to think about whether to participate.

We will apply the eligibility standard listed on the next page to determine if you qualify to participate in the study. If you qualify, we will ask you to consider signing this document to indicate your consent to participate. Your signing indicates your willingness to participate in this study, but you would still be free to withdraw from the study at any time, without having to give a reason.

Test subject's initials:.....

Date:.....

If you decide you would like to participate, initial each page of this form and sign the last page in the presence of the ICR staff. The Principal Investigator will sign the form as well, and you will be given a copy with both signatures. We will notify you by phone within one week whether you have been selected for the study.

**Eligibility for the Study**

To participate in this study you must meet the following conditions:

- Sex: Six of each: Male and Female (plus one extra of either sex)
- Age: You must be at least 18 and not over 70
- Race: No exclusions
- Literacy: You must be able to read, speak, and understand English
- You must be attractive to stable flies, as evidenced by at least 2 landings of caged stable flies on your untreated forearm within one minute.
- You must not be pregnant or breastfeeding. If you are female, you will be required to perform an over-the-counter urine pregnancy test on the morning of the study. ICR will provide the test kit, and a female ICR staff member will verify the results. ICR will keep the results of the pregnancy test confidential from everyone except you and the Principal Investigator.
- You must not be an employee or a relative of an employee of ICR Inc., LANXESS Corporation, or any other party with an interest in this research.
- You must have no known sensitivity to stable fly bites, to insect repellents, or to skin care products

If you choose to participate in this study and are selected to be a study subject, you must also agree

- To follow the directions of the Principal Investigator and other ICR staff.
- Not to use tobacco, alcohol, or any scented cosmetic products after 8 p.m. the night before the study, and on the day of the study until it is concluded.
- To wear proper protective clothing on the day of the study: blue jeans or other sturdy

Test subject's initials:.....

Date:.....

trousers, heavy socks, long sleeve shirts, and gloves. Gloves will be provided by ICR. The heavy clothing will help protect you from any stable flies which escape from the cages during testing.

**Laboratory Repellent Phase Summary**

Thirteen subjects will participate in this one-day laboratory study over a period of about 11 hours. One of you will be selected by chance (like pulling a number out of a hat) to serve as the "control subject", and will not be treated with the test repellents. The other 12 subjects will be "treated subjects", and will be treated with both of the repellents, one on each forearm. The entire test will be conducted in a room maintained at comfortable temperature and humidity.

Every 30 minutes during the test, the untreated control subject will put one untreated forearm into each test cage containing 25 stable flies for one minute. If fewer than 2 stable flies land within one minute, the stable flies will be vacuumed from all 6 test cages and 25 more stable flies will be added to each cage to ensure enough activity for a valid test.

After the untreated control subject has verified adequate stable fly activity, the 12 treated subjects will carefully put both forearms into their assigned cage with the stable flies for five minutes.

This pattern will be continued every half hour until you receive either two stable fly bites on the same arm in the same 5-minute exposure period, or one bite in each of two consecutive 5-minute exposure periods, or until ten hours after your treatment, whichever happens first.

**Procedures**

On the day of the study, before the test begins:

- We will review this document with you and answer any additional questions you may have since you have signed it.
- You will wash your arms with unscented Neutrogena®® soap.
- We will measure and mark a 3 to 5 inch wide test area around each of your forearms as described in detail below.

Test subject's initials:.....

Date:.....

- After we have measured your arms and protected the skin outside the test area, we will determine your attractiveness to stable flies as described below.

- Unless you are selected as the untreated control subject, we will treat both your arms with test repellents and the study will begin.

**Here is how that will work in detail**

**Laboratory Study Details**

1. One of you will be selected by chance (like pulling a number out of a hat) to be the untreated control subject.

2. We will measure the distance around your arm at the wrist and the elbow, and calculate how wide a band is needed for the standard test area on your arm. This 3 - 5 inch wide band will be wider on thinner arms; narrower on bigger arms. We will then use a felt-tip pen to mark the location of the band around each of your forearms. The control subject will be measured and marked on only one forearm.

3. We will protect the skin above and below the marked test area from stable fly bites with multiple layers of elastic bandages and or Velcro® straps held in place with adhesive tape.

4. We will verify that you are attractive to stable flies. You will put one forearm into a test cage containing 25 stable flies, and we will count the number of stable flies landing on your arm. We will brush landing stable flies off your arm before they have a chance to bite you. If 2 stable flies land on your arm in a minute or less you will qualify as "attractive". You will then repeat the same procedure with your other arm. If you are not attractive after one attempt, you may repeat the process a second time. If you fail to attract stable flies in two trials you may not be eligible to participate in the study.

5. If you are a treated subject, we will apply one of the repellents to the test area on each of your forearms, using a syringe without the needle. The amount of repellent applied will be a standardized "typical consumer dose". This amount will always be less than a quarter of a teaspoonful. If you are the untreated control subject, you will receive no treatment.

Test subject's initials:.....

Date:.....

6. With a fingertip in a latex or vinyl glove, we will spread the repellent evenly over the test areas. Once your arms have been treated, you must be careful not to rub them against anything, as this could rub off some of the test repellent and change the results of the study.

7. We will mark your bandages with a letter identifying the repellent applied to that arm. We will not identify the repellents to you.

8. You will go to the test laboratory and wait for your repellents to dry for about one-half hour. Then you will put on gloves to protect your hands from bites, ready for your first 5-minute exposure period of the day.

9. ICR staff will show you which cage to use. Treated subjects will work in pairs. If you see a stable fly land on your own or your partner's arm, notify ICR staff.

10. Every 30 minutes after the test begins, the untreated control subject will put one arm into each of the six test cages in turn, to verify stable fly activity. As soon as 2 stable flies land, the control subject will remove his or her arm from the cage. If fewer than 2 stable flies land on the control subject's arm within one minute, all of the flies in each of the 6 test cages will be vacuumed out and replaced with 25 fresh stable flies. ICR staff will brush away any landing stable flies from the control subject before the flies have time to bite. Nonetheless, it is likely that the control subject will get some bites during the course of the study.

11. Every 30 minutes after the study begins, after the activity of the stable flies in their assigned cage has been verified, each pair of treated subjects will carefully put both their arms into the cage for 5 minutes. During the 5-minute exposure period we will count the number of stable flies (up to two) that bite the treated skin of either of your arms. When you receive two bites on the same arm in one exposure period, or one bite in each of two consecutive exposure periods, you will remove that arm from the cage and from the study. We will call this "breakdown", and once you reach breakdown on one of your arms you will no longer expose that arm for the rest of the day's study. You can then remove the bandages and tape from this arm, and scratch if you choose. Caladryl®, Calamine® lotion and rubbing alcohol will be

Test subject's initials:.....

Date:.....

provided to help stop any itching from bites you received. When you reach breakdown on both arms, you will have finished your part in the study and may go home.

12. After each 5-minute exposure period you may leave the test room, but you must remain in the lab. You can go to the restroom if you need to, and the Study Director will call breaks every few hours. You may either bring your own lunch or pay to have lunch ordered.

13. After preparation and treatment of subjects, which will take about one hour, the day's study will include up to twenty 5-minute exposure periods at 30 minute intervals over 10 hours. The study will end after 10 hours or when all treated test subjects have reached breakdown on both arms, whichever comes first.

**Discomfort and Hazard**

**Stable fly bites**

A bite occurs when a stable fly lands and sticks its pointed mouthparts into your skin and takes blood. A stable fly bite will cause momentary pain and leave a small red mark which will usually disappear within a couple of days. The pain from a stable fly bites usually stops as soon as it stops biting. The irritation and swelling, which often result from mosquito bites, are not nearly so common after stable fly bites. In severe cases, a bite or probe may cause the development of large bumps on your skin, difficulty breathing, sweating and/or a rapid pulse. For some people this could be life-threatening.

All subjects will be exposed to stable flies for at least 1 minute to verify attractiveness to stable flies. Although we will try to brush the stable flies off before they bite, there is a slight possibility of being bitten. Treated subjects will expose their forearms to stable flies for five minutes every half hour. Although they will not expose an arm further if they receive two bites on it in one exposure, or one bite in two consecutive exposure periods, they may receive more than two bites on each arm during the test. A bite which is not followed by another bite in the same or the next exposure will be disregarded. If you are a treated subject you will still need to receive at least two more bites on that arm to reach breakdown. The untreated control subject will be exposed to stable flies every half hour for up to one minute in each of six test cages. Although we will try to

brush the landing stable flies off before they bite, the control subject is likely to be bitten by some of them. We will minimize the irritation from bites or probes you receive by making Caladryl® or Calamine® lotion or rubbing alcohol available at the study site for your use after the study is completed.

**Reaction to the test repellents**

You may have a reaction to the test repellents.

The Sponsor has minimized this possibility by choosing an active ingredient (picaridin) that has demonstrated low oral, skin, and inhalation toxicity. The Environmental Protection Agency (EPA) has classified it as low toxicity for acute inhalation toxicity and primary skin irritation. EPA has classified the two test repellents as having low to mild toxicity based on eye irritation. For this reason it is important not to rub your eyes with your treated arms. The Sponsor has selected the non-repellent ingredients in the formulations because they are widely used in cosmetics and have a long history of safe use. ICR staff will be monitoring all subjects for any signs of a reaction to the test repellents. If you think you may be having such a reaction, tell a member of the staff immediately. A reaction may include redness, irritation, burning, swelling or a rash.

The stable flies being used in this study will be laboratory-reared and disease-free, and they will never have had a human blood meal. There is therefore no risk of your contracting any stable fly-borne disease as a result of participation in this study.

Should you have any medical problems, we will have First- Aid- qualified staff members, and supplies on site. We will have cell phones to make emergency calls if necessary. In the case of medical emergency, we will transport you to a selected local hospital at our expense. We will pay all of your medical bills for study-related illnesses and injuries. The Principal Investigator will contact you by telephone, two weeks after the study to ask if you have experienced any adverse effects. You should contact the Principal Investigator any time after the study if you experience any study-related adverse effects, either before or after this follow up call.

**Financial Consideration**

We will pay you $11/hour for the first 9 hours and $17.50 for each additional hour that you spend on the day of the study. The study will last about 10 hours with an additional hour of prep time (11

Test subject's initials:.....

Date:.....

hours total), with a total payment of $134. This payment will be mailed to you on the 15th or the last day of the month. If we ask you to drop out of the test, and you have complied with all of our requests, you will still receive full payment. If we ask you to drop out of the test because you have not followed all of our directions, or if you choose to drop out of the test, we will compensate you for time up to that point at the rate of $11 per hour.

**Costs**

There are no financial costs to you for participating in this study.

**Benefits**

You will get no personal benefit from participating in this study.
Some benefit may result for society in general through showing the effectiveness of these products in repelling a noxious pest.

**Your Rights**

We will give you an opportunity to discuss with us any aspects of this document or of the study it describes that are not clear to you, so that you fully understand the nature of the study, its purpose, and the procedures to be used, as well as the discomforts, and risks you may experience during or after the study. You are encouraged to ask questions at any time, before or after you consent to participate, and before, during, or after the study day itself. Your participation is entirely voluntary. You may decide not to take part in this study, and if you decide you would like to participate, you are free to change your mind at any time without having to explain, and without penalty or loss of benefits to which you may be otherwise entitled.

**Alternative**

The only alternative is not to participate.

**New Information**

You will be informed verbally or in writing of any significant new findings discovered during the course of this study which may influence your continued participation.

Test subject's initials:.....

Date:.....

**Voluntary Participation/Withdrawal**

You may be withdrawn from the study even if you want to continue. This could happen if (1) the study director believes it is in your best interest for you to stop being in the study, (2) or if you do not follow instructions for the study, (3) or if the sponsor stops the study for administrative or any other reasons.

**Questions**

If you have any questions about this study or suffer a reaction you think might be associated with the study, call us at 410-747-4500. If you have any questions about your rights as a research participant, or related concerns, you may contact the Essex Institutional Review Board (IRB), 121 Main Street, Lebanon, NJ 08833, telephone 908-236-7735. The Essex IRB is a committee that has reviewed this research project to help ensure that the rights and welfare of the participants are protected and that the study is designed and carried out ethically. Review of this study by the Essex IRB is not an endorsement of the study or its outcome.

**Research Participation Information**

You can obtain information about participating in research studies from a number of sources.
A few are:

- Center of Information and Study on Clinical Research Participation (CISCRP): www.ciscrp.org
- Food and Drug Administration (FDA): www.fda.gov
- Office for Human Research Protections (OHRP): www.hhs.gov/ohrp
- National Institute of Health: www.clinicaltrials.gov
- National Cancer Institute: www.nei.nih.gov
- Center Watch: www.centerwatch.com
- Various large university websites
- Various associations and societies concerned with specific diseases websites.

Test subject's initials:.....

Date:.....

**Confidentiality**

We and the sponsor or its agents may use the information obtained from your taking part in this test, and this information may become part of a report. We will keep your participation as confidential as possible referring to you in the study data and reports only by your initials or an arbitrary ICR identification. However, we cannot guarantee that your identity will be kept confidential; the sponsor, personnel associated with the study, a regulatory agency such as the Environmental Protection Agency (EPA), and the Essex Institutional Review Board (EIRB) all have a right to review your records.

**Consent**

I voluntarily agree to participate in this study. I will be given a copy of this signed form.
By signing this form I have not given up any of my legal rights.

_____
Printed Name of Subject

_____
Signature of Subject Date

_____
Signature of Person Obtaining Consent Date

_____
Signature of Principal Investigator Date

Test subject's initials:.....

Date:.....

## APPENDIX IV:
## LABELS FOR PRODUCTS

Test subject's initials:.....

Date:.....

# KBR 3023 Insect Repellent Cream

**Contains Bayrepel™. Long-lasting, effective protection from mosquitoes ticks, biting flies, gnats, chiggers, sand 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**

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

LANXESS

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

### 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.

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

ACCEPTED
with COMMENTS
In EPA Letter Dated
APR 10 2007
Under the Federal Insecticide, Fungicide, and Rodenticide Act, as amended, for the pesticide registered under EPA Reg. No. 39967-50

LABEL TEXT DATED:

PAGE 00092 OF 00376
55 of 76

# KBR 3023 All-Family Insect Repellent Spray

**Long-lasting, effective protection from mosquitoes, ticks, biting flies, gnats, chiggers, sand flies, 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.:**

ACCEPTED
APR 16 2007
Under the Federal Insecticide, Fungicide, and Rodenticide Act, as amended, for the pesticide Registered under EPA Reg. No. 39967-53

LANXESS

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

LABEL TEXT DATE:

## APPENDIX V:
## PRODUCT TOXICOLOGY

Test subject's initials:.....

Date:.....

**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 I4-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 $_{a2u}$ globulin accumulation. The toxicology profile by oral route of exposure did not reveal any new targets compared to the dermal route and. 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/200rng/kg/day- the highest dose tested).

Test subject's initials:.....

Date:.....

## 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

## APPENDIX VI: RECRUITMENT SCRIPT

Repellent Test Recruitment Telephone Script
Protocol Number: G4330108001A382
Protocol Version Date: February 1, 2008
Subject Initials/#:

**ICR will be conducting a stable fly repellent study and a dose determination study for the this main repellent study on these dates, (Month, Day(s), Year). The location of these studies will be the ICR laboratory at 1330 Dillon Heights Avenue, Catonsville, Maryland. Will you be available on these dates?**

***If the person is available the inclusion/exclusion criteria will be discussed to verify whether the person qualifies to participate.***

**I will now read the inclusion criteria to you to see if you qualify to participate in the study.**

Inclusion Criteria:
**Please let me know if you do not satisfy any of the following inclusion criteria:**

**We will accept an equal number of male and female participants.**
**You must be between 18 and 70 years old.**
**There are no race restrictions.**
**You must be able to read, speak, and understand English.**
**You must consider yourself to be in good health.**
**For the repellent study only, you must be attractive to stable flies. We must verify this in the lab by inserting your untreated forearm into a cage of stable flies to see if at least 2 stable flies land within one minute.**

**I will now read the exclusion criteria to you to see if you do not qualify to participate in the study.**

Exclusion Criteria:
**Please let me know if you can satisfy the following exclusion criteria:**

**You cannot participate if you are pregnant or breastfeeding. All female subjects will be required to perform a urine OTC pregnancy test on the morning of the study.**

**You cannot participate if you are an employee or a relative of an employee of ICR Inc., the sponsor, toXcel, LLC, or any interested party.**

**For the repellency test only, you cannot participate if you are sensitive to stable fly bites.**

**You cannot participate if you have any known sensitivity to insect repellents or skin care products.**

*If an individual elects to participate in the study, after they have satisfied the inclusion/exclusion criteria, they must agree to the following:*

**I will now read a list of items that you must agree to in order to participate in the study. You must agree to follow the directions of the Principal Investigator and other ICR staff.**

**You must agree to abstain from the use of tobacco, alcohol, and all scented cosmetic products after 8 p.m. the night before the study, and on the day of the study until it is concluded.**

**For the repellent study only, you must agree to wear proper protective clothing such as blue jeans, heavy socks, long sleeve shirt, and gloves (gloves provided by ICR).**

*If an individual elects to participate in the study, after they have satisfied the inclusion/exclusion criteria and agree to follow the above we will then discuss the test with them.*

STABLE FLY REPELLENT STUDY

**You will be one of thirteen subjects who participate in this one-day laboratory study lasting about 11 hours. One of you will be selected by chance to serve as the "control subject", and will not be treated with the test repellents. The other 12 of you will be "treated subjects", and will be treated with both of the repellents, one on each forearm.**

**Every 30 minutes during the test, the untreated control subject will put one untreated forearm into each test cage containing 25 stable flies for one minute. If fewer than 2 stable flies land within one minute, these stable flies will be vacuumed from the cage and 25 more stable flies will be added to each cage to ensure enough activity for a valid test.**

**After the untreated control subject has verified adequate mosquito activity, the 12 treated subjects will carefully put both forearms into their assigned cage with the stable flies for five minutes.**

**This pattern will be continued every half hour until you receive either two stable fly bites on the same arm in the same 5-minute exposure period, or one bite in each of two consecutive 5-minute exposure periods, or until ten hours after your treatment, whichever happens first.**

DOSE DETERMINATION STUDY

**You will be one of twelve subjects who will participate in this one-day laboratory study**

**lasting probably less than 4 hours. Each of you will apply the two test repellents (a cream and a spray) three times to a marked out area of your forearm. We will measure the amount of repellent you and the other eleven subjects apply and average these amounts to determine how much repellent will be applied in the subsequent repellent study.**

***If an individual is still interested in participating in either study, we will discuss the ICD with them.***

**You are being asked to participate in a research study. Before agreeing to participate in this study, it is important that you read a form. This form is called an informed consent document. The informed consent document describes the purpose, procedures, benefits, financial payment, risks and discomforts of the study. It also describes the alternative procedures that are available to you and your right not to participate or to withdraw from the study at anytime. Please ask as many questions as you need to so that you can decide whether you want to be in the study. After reading this and having all questions answered, if you decide to participate, you should return this consent form to the to the study director. Sign the last page, initial and date each prior page in the presence of the study staff. You may refuse to participate in this study and this decision will not be held against you. If you are still interested in participating in the study we will mail an informed consent document to you for your review. In addition, after you have read the informed consent document, we would like you to come to the ICR office in person so that we can discuss the informed consent document with you and answer any questions that you may have. However if you are not able to visit our office prior to the study date, you must subsequently sign the ICD on the morning of the study at the ICR laboratory if you still wish to participate in the study.**

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**PROTOCOL:** EVALUATION OF THE EFFICACY OF KBR 3023 (PICARIDIN; ICARIDIN) – BASED PERSONAL INSECT REPELLENTS (20% CREAM, 20% SPRAY) AGAINST STABLE FLIES IN THE LABORATORY

## INFORMED CONSENT AUTHORIZATION TO PARTICIPATE IN THE DOSE DETERMINATION PHASE OF AN ICR, INC. STABLE FLY REPELLENT EVALUATION IN THE LABORATORY

**Principal Investigator: William J. Gaynor**
**Address: ICR, Inc. 1330 Dillon Heights Ave. Baltimore, MD**
**Telephone Number: 410-747-4500**
**24 Hour Emergency Number: 410-207-0415**



### Purpose of Study

We (ICR, Inc.) have been contracted by LANXESS Corporation to conduct a research study in our laboratory on two insect repellent products containing the active ingredient picaridin, to find out how well these products repel stable flies. Before this study can be performed the dose of the two repellents to be used in the study must be determined based on how much product a typical consumer would apply to themselves. This dose determination phase of the study is the study for which we are asking you for your participation. This dose determination phase of the study will occur in the ICR, Inc. lab where the stable fly repellents will later be tested using the doses you determine today. We have prepared this Informed Consent Document (ICD) to explain this dose determination study to you so that you can make a free choice whether or not to participate.

We will review this document with you to make sure you understand what would be expected of you if you participate, and to explain the risks you would face through your participation. Please ask us about anything you do not understand. If you have have come into our office to review the document, you may take it home with you if you need more time to think about whether to participate.

Test subject's initials:.....

Date:.....

We will apply the eligibility standard listed below to determine if you qualify to participate in the study. If you qualify, we will ask you to consider signing this document to indicate your consent to participate. Your signing indicates your willingness to participate in this study, but you would still be free to withdraw from the study at any time, without having to give a reason.

If you decide you would like to participate, initial each page of this form and sign the last page in the presence of the ICR staff. The Principal Investigator will sign the form as well, and you will be given a copy with both signatures. We will notify you by phone within one week whether you have been selected for the study.

**Eligibility for the Study**

To participate in this study you must meet the following conditions:

- Sex: Six of each: Male and Female
- Age: You must be at least 18 and not over 70
- Race: No exclusions
- Literacy: You must be able to read, speak, and understand English
- You must not be pregnant or breastfeeding. If you are female, you will be required to perform an over-the-counter urine pregnancy test on the morning of the study. ICR will provide the test kit, and a female ICR staff member will verify the results. ICR will keep the results of the pregnancy test confidential from everyone except you and the Principal Investigator.
- You must not be an employee or a relative of an employee of ICR Inc., LANXESS Corporation, or any other party with an interest in this research.
- You must have no known sensitivity to insect bites/stings, repellents or to skin care products

If you choose to participate in this study and are selected to be a study subject, you must also agree:

Test subject's initials:.....

Date:.....

- To follow the directions of the Principal Investigator and other ICR staff.

- Not to use tobacco, alcohol, or any scented cosmetic products after 8 p.m. the night before study, and on the day of the study until it is concluded.

**Dose Determination Phase Summary**

Twelve subjects will participate in this one-day laboratory study. Each of you will apply the cream repellent and the spray repellent to your arms three times. You will apply as much as you normally would, without any instructions from us as to how much to apply. We will measure the amount of repellent you applied and average that amount with the amount the other participants applied to determine the dose to be used in the repellent study. This study will take less than 9 hours for all 12 test subjects. If you finish early, you will be allowed to leave earlier. The entire test will be conducted in a room maintained at comfortable temperature and humidity.

**Procedures**

On the day of the study, before the test begins:

- We will review this document with you and answer any additional questions you may have since you have signed it.

- You will wash your arms with unscented Neutrogena® soap.

- We will measure and mark a 3 to 5 inch wide test area around each of your forearms as described in detail below.

- You will apply the spray and cream repellents three times to the treated area of your forearms in the amount that you would normally apply.

- We will weigh the amount of repellents you and the other 11 test subjects applied and average them to determine a testing dose.

Test subject's initials:.....

Date:.....

**Here is how that will work in detail**

**Laboratory Study Details**

1. All 12 of you will be involved in treating your forearms with each of the two repellent products. You must not observe or discuss with other subjects any of these procedures.

2. We will measure the distance around your arm at the wrist and the elbow, and calculate how wide a band is needed for the standard test area on your arm. This 3 - 5 inch wide band will be wider on thinner arms; narrower on bigger arms. We will then use a felt-tip pen to mark the location of the band around each of your forearms.

3. We will cover the skin above and below the marked test area with multiple layers of elastic bandages and or Velcro® straps held in place with adhesive tape.

4. You will then put on a latex or vinyl glove and use a gloved finger to apply the cream repellent to the treatment area of your forearm until you feel you have applied the amount of repellent you would apply if you were applying it at home.

5. We will determine how much product you applied by weighing the repellent container before and after you use it.

6. You will apply the cream repellent a total of three times in the same way. Between applications you will wash your forearm with unscented Neutrogena soap until you feel that you have washed off all the repellent. You will then dry your arm with a paper towel and then let it air dry until your arm feels completely dry.

7. We will then measure the amount of the spray repellent you would typically apply. We will take an average of your three applications and of all the other subjects. Finally we will take an average of these 12 subject averages.

Test subject's initials:.....

Date:.....

8. We will wrap a 2 inch wide strip of waterproof dressing around the middle of the test area on your arm (waterproof side against your skin). Then we will wrap a 2 inch wide band of surgical gauze around the dressing. We will secure the gauze and the dressing with two rubber bands. Your forearm will now have a band of dressing (with gauze on top) and bare skin on either side.

9. You will then spray the second repellent over the entire marked out treatment band area of your forearm (including the gauze-covered dressing) until the amount of product you have applied to the two bare skin areas of your forearm feels like what you would apply if you were using the product at home.

10. We will remove the gauze-covered dressing and weigh it to calculate the amount of product you applied.

11. You will repeat this spraying process two more times, washing and drying your forearm as you did with the cream repellent between applications. We will use new bands of dressing and gauze for each of the three sprayings.

12. Once you have applied both the cream and repellents three times, your involvement in the test is done. You may remove your bandages, wash your forearms, and go home.

13. The day's study may last up to nine hours for all 12 test subjects, although your direct involvement should not last more than three hours. You may either bring your own lunch or pay to have lunch ordered.

Test subject's initials:.....

Date:.....

**Discomfort and Hazard**

**Reaction to the test repellents:**

You may have a reaction to the test repellents.

The Sponsor has minimized this possibility by choosing an active ingredient (picaridin) that has demonstrated low oral, skin, and inhalation toxicity. The Environmental Protection Agency (EPA) has classified it as low toxicity for inhalation toxicity and primary skin irritation. EPA has classified the two test repellents as having low to mild toxicity based on eye irritation. For this reason it is important not to rub your eyes with your treated arms. The Sponsor has selected the non-repellent ingredients in the formulations because they are widely used in cosmetics and have a long history of safe use. ICR staff will be monitoring all subjects for any signs of a reaction to the test repellents. If you think you may be having such a reaction, tell a member of the staff immediately. A reaction may include redness, irritation, burning, swelling or a rash.

Should you have any medical problems, we will have First- Aid- qualified staff members and supplies on site. We will have cell phones to make emergency calls if necessary. In the case of medical emergency, we will transport you to a selected local hospital at our expense. We will pay all of your medical bills for study-related illnesses and injuries. The Principal Investigator will contact you by telephone, two weeks after the study to ask if you have experienced any adverse effects. You should contact the Principal Investigator any time after the study if you experience any study-related adverse effects, either before or after this follow up call.

**Financial Consideration**

We will pay you $11/hour for the 9-hour duration of the study for a total payment of $99. This payment will be mailed to you on the 15$^{th}$ or the last day of the month. If we ask you to drop out of the test, and you have complied with all of our requests, you will still receive full payment. If we ask you to drop out of the test because you have not followed all of our directions, or if you choose to drop out of the test, we will compensate you for time up to that point at the rate of $11 per hour.

Test subject's initials:.....

Date:.....

**Costs**

There are no financial costs to you for participating in this study.

**Benefits**

You will get no personal benefit from participating in this study. The main benefit of this dose determination study is that it establishes the dose of the repellents to be tested in the subsequent stable fly repellent study. Some benefit may result for society in general through showing the effectiveness of these products in repelling a noxious pest.

**Your Rights**

We will give you an opportunity to discuss with us any aspects of this document or of the study it describes that are not clear to you, so that you fully understand the nature of the study, its purpose, and the procedures to be used, as well as the discomforts, and risks you may experience during or after the study. You are encouraged to ask questions at any time, before or after you consent to participate, and before, during, or after the study day itself. Your participation is entirely voluntary. You may decide not to take part in this study, and if you decide you would like to participate, you are free to change your mind at any time without having to explain, and without penalty or loss of benefits to which you may be otherwise entitled.

**Alternative**

The only alternative is not to participate.

**New Information**

You will be informed verbally or in writing of any significant new findings discovered during the course of this study which may influence your continued participation.

Test subject's initials:.....

Date:.....

**Voluntary Participation/Withdrawal**

You may be withdrawn from the study even if you want to continue. This could happen if (1) the study director believes it is in your best interest for you to stop being in the study, (2) or if you do not follow instructions for the study, (3) or if the sponsor stops the study for administrative or any other reasons.

**Questions**

If you have any questions about this study or suffer a reaction you think might be associated with the study, call us at 410-747-4500. If you have any questions about your rights as a research participant, or any related concerns or complaints, you may contact the Essex Institutional Review Board (IRB), 121 Main Street, Lebanon, NJ 08833, telephone 908-236-7735. The Essex IRB is a committee that has reviewed this research project to help ensure that the rights and welfare of the participants are protected and that the study is designed and carried out ethically. Review of this study by the Essex IRB is not an endorsement of the study or its outcome.

**Research Participation Information**

You can obtain information about participating in research studies from a number of sources.
A few are:

- Center for Information and Study on Clinical Research Participation (CISCRP); www.ciscrp.org
- Food and Drug Administration (FDA): www.fda.gov
- Office for Human Research Protections (OHRP): www.hhs.gov/ohrp
- National Institute of Health: www.clinicaltrials.gov
- National Cancer Institute: www.nci.nih.gov
- Center Watch: www.centerwatch.com
- Various large university websites
- Various associations and societies concerned with specific diseases websites.

Test subject's initials:.....

Date:.....

**Confidentiality**

We and the sponsor or its agents may use the information obtained from your taking part in this test, and this information may become part of a report. We will keep your participation as confidential as possible referring to you in the study data and reports only by your initials or an arbitrary ICR identification. However, we cannot guarantee that your identity will be kept confidential; the sponsor, personnel associated with the study, a regulatory agency such as the Environmental Protection Agency (EPA), and the Essex Institutional Review Board (EIRB) all have a right to review your records.

**Consent**

I voluntarily agree to participate in this study. I will be given a copy of this signed form. By signing this form I have not given up any of my legal rights.

_____
Printed Name of Subject

_____
Signature of Subject Date

_____
Signature of Person Obtaining Consent Date

_____
Signature of Principal Investigator Date

Test subject's initials:.....

Date:.....

**PROTOCOL:** EVALUATION OF THE EFFICACY OF KBR 3023 (PICARIDIN; ICARIDIN) – BASED PERSONAL INSECT REPELLENTS (20% CREAM, 20% SPRAY) AGAINST STABLE FLIES IN THE LABORATORY

## INFORMED CONSENT AUTHORIZATION TO PARTICIPATE IN AN ICR, INC. STABLE FLY REPELLENT EVALUATION IN THE LABORATORY

**Principal Investigator: William J. Gaynor**
**Address: ICR, Inc. 1330 Dillon Heights Ave. Baltimore, MD**
**Telephone Number: 410-747-4500**
**24 Hour Emergency Number: 410-207-0415**



**Purpose of Study**

We (ICR, Inc.) have been contracted by LANXESS Corporation to conduct a research study in our laboratory on two insect repellent products containing the active ingredient picaridin, to find out how well these products repel stable flies. The stable flies used in this study are laboratory-reared and do not carry any diseases. This study will take place in the ICR, Inc. lab with stable flies confined in cages. This document will explain the study to you so that you can make a free choice whether or not to participate.

We will review this document with you to make sure you understand what would be expected of you if you participate, and to explain the risks you would face through your participation. Please ask us about anything you do not understand. If you have have come into our office to review the document, you may take it home with you if you need more time to think about whether to participate.

We will apply the eligibility standard listed on the next page to determine if you qualify to participate in the study. If you qualify, we will ask you to consider signing this document to indicate your consent to participate. Your signing indicates your willingness to participate in this study, but you would still be free to withdraw from the study at any time, without having to give a reason.

Test subject's initials:.....

Date:.....

If you decide you would like to participate, initial each page of this form and sign the last page in the presence of the ICR staff. The Principal Investigator will sign the form as well, and you will be given a copy with both signatures. We will notify you by phone within one week whether you have been selected for the study.

**Eligibility for the Study**

To participate in this study you must meet the following conditions:

- Sex: Six of each: Male and Female (plus one extra of either sex)
- Age: You must be at least 18 and not over 70
- Race: No exclusions
- Literacy: You must be able to read, speak, and understand English
- You must be attractive to stable flies, as evidenced by at least 2 landings of caged stable flies on your untreated forearm within one minute.
- You must not be pregnant or breastfeeding. If you are female, you will be required to perform an over-the-counter urine pregnancy test on the morning of the study. ICR will provide the test kit, and a female ICR staff member will verify the results. ICR will keep the results of the pregnancy test confidential from everyone except you and the Principal Investigator.
- You must not be an employee or a relative of an employee of ICR Inc., LANXESS Corporation, or any other party with an interest in this research.
- You must have no known sensitivity to stable fly bites, to insect repellents, or to skin care products.
- If you choose to participate in this study and are selected to be a study subject, you must also agree:
- To follow the directions of the Principal Investigator and other ICR staff.
- Not to use tobacco, alcohol, or any scented cosmetic products after 8 p.m.

Test subject's initials:.....

Date:.....

the night before study, and on the day of the study until it is concluded.

- To wear proper protective clothing on the day of the study: blue jeans or other sturdy trousers, heavy socks, long sleeve shirts, and gloves. Gloves will be provided by ICR. The heavy clothing will help protect you from any stable flies which escape from the cages during testing.

**Laboratory Repellent Phase Summary**

Thirteen subjects will participate in this one-day laboratory study over a period of about 11 hours. One of you will be selected by chance (like pulling a number out of a hat) to serve as the "control subject", and will not be treated with the test repellents. The other 12 subjects will be "treated subjects", and will be treated with both of the repellents, one on each forearm. The entire test will be conducted in a room maintained at comfortable temperature and humidity.

Every 30 minutes during the test, the untreated control subject will put one untreated forearm into each test cage containing 25 stable flies for one minute. If fewer than 2 stable flies land within one minute, the stable flies will be vacuumed from all 6 test cages and 25 more stable flies will be added to each cage to ensure enough activity for a valid test.

After the untreated control subject has verified adequate stable fly activity, the 12 treated subjects will carefully put both forearms into their assigned cage with the stable flies for five minutes.

This pattern will be continued every half hour until you receive either two stable fly bites on the same arm in the same 5-minute exposure period, or one bite in each of two consecutive 5-minute exposure periods, or until ten hours after your treatment, whichever happens first.

**Procedures**

On the day of the study, before the test begins:

- We will review this document with you and answer any additional questions you

Test subject's initials:.....

Date:.....

may have since you have signed it.

- You will wash your arms with unscented Neutrogena® soap.
- We will measure and mark a 3 to 5 inch wide test area around each of your forearms as described in detail below.
- After we have measured your arms and protected the skin outside the test area, we will determine your attractiveness to stable flies as described below.
- Unless you are selected as the untreated control subject, we will treat both your arms with test repellents and the study will begin.

**Here is how that will work in detail**

**Laboratory Study Details**

1. One of you will be selected by chance (like pulling a number out of a hat) to be the untreated control subject.

2. We will measure the distance around your arm at the wrist and the elbow, and calculate how wide a band is needed for the standard test area on your arm. This 3 - 5 inch wide band will be wider on thinner arms; narrower on bigger arms. We will then use a felt-tip pen to mark the location of the band around each of your forearms. The control subject will be measured and marked on only one forearm.

3. We will protect the skin above and below the marked test area from stable fly bites with multiple layers of elastic bandages and or Velcro® straps held in place with adhesive tape.

4. We will verify that you are attractive to stable flies. You will put one forearm into a test cage containing 25 stable flies, and we will count the number of stable flies landing on your arm. We will brush landing stable flies off your arm before they have a chance to bite you. If 2 stable flies land on your arm in

a minute or less you will qualify as "attractive". You will then repeat the same procedure with your other arm. If you are not attractive after one attempt, you may repeat the process a second time. If you fail to attract stable flies in two trials you may not be eligible to participate in the study.

5. If you are a treated subject, we will apply one of the repellents to the test area on each of your forearms, using a syringe without the needle. The amount of repellent applied will be a standardized "typical consumer dose". This amount will always be less than a quarter of a teaspoonful. If you are the untreated control subject, you will receive no treatment.

6. With a fingertip in a latex or vinyl glove, we will spread the repellent evenly over the test areas. Once your arms have been treated, you must be careful not to rub them against anything, as this could rub off some of the test repellent and change the results of the study.

7. We will mark your bandages with a letter identifying the repellent applied to that arm. We will not identify the repellents to you.

8. You will go to the test laboratory and wait for your repellents to dry for about one-half hour. Then you will put on gloves to protect your hands from bites, ready for your first 5-minute exposure period of the day.

9. ICR staff will show you which cage to use. Treated subjects will work in pairs. If you see a stable fly land on your own or your partner's arm, notify ICR staff.

10. Every 30 minutes after the test begins, the untreated control subject will put one arm into each of the six test cages in turn, to verify stable fly activity. As soon as 2 stable flies land, the control subject will remove his or her arm from the cage. If fewer than 2 stable flies land on the control subject's arm within one minute, all of the flies in each of the 6 test cages will be vacuumed out and replaced with 25 fresh stable flies. ICR staff will brush away any landing stable flies from the control subject before the flies have time to bite. Nonetheless, it is likely that the control subject will get some bites during the course of the study.

Test subject's initials:.....

Date:.....

11. Every 30 minutes after the study begins, after the activity of the stable flies in their assigned cage has been verified, each pair of treated subjects will carefully put both their arms into the cage for 5 minutes. During the 5-minute exposure period we will count the number of stable flies (up to two) that bite the treated skin of either of your arms. When you receive two bites on the same arm in one exposure period, or one bite in each of two consecutive exposure periods, you will remove that arm from the cage and from the study. We will call this "breakdown", and once you reach breakdown on one of your arms you will no longer expose that arm for the rest of the day's study. You can then remove the bandages and tape from this arm, and scratch if you choose. Caladryl®, Calamine® lotion and rubbing alcohol will be provided to help stop any itching from bites you received. When you reach breakdown on both arms, you will have finished your part in the study and may go home.

12. After each 5-minute exposure period you may leave the test room, but you must remain in the lab. You can go to the restroom if you need to, and the Study Director will call breaks every few hours. You may either bring your own lunch or pay to have lunch ordered.

13. After preparation and treatment of subjects, which will take about one hour, the day's study will include up to twenty 5-minute exposure periods at 30 minute intervals over 10 hours. The study will end after 10 hours or when all treated test subjects have reached breakdown on both arms, whichever comes first.

**Discomfort and Hazard**

**Stable fly bites**

A bite occurs when a stable fly lands and sticks its pointed mouthparts into your skin and takes blood. A stable fly bite will cause momentary pain and leave a small red mark which will usually disappear within a couple of days. The pain from a stable fly bites usually stops as soon as it stops biting. The irritation and swelling, which often result from mosquito bites, are not nearly so common after stable fly bites. In severe cases, a bite or probe may cause the development of large bumps on your skin, difficulty

breathing, sweating and/or a rapid pulse. For some people this could be life-threatening.

All subjects will be exposed to stable flies for at least 1 minute to verify attractiveness to stable flies. Although we will try to brush the stable flies off before they bite, there is a slight possibility of being bitten.

Treated subjects will expose their forearms to stable flies for five minutes every half hour. Although they will not expose an arm further if they receive two bites on it in one exposure, or one bite in two consecutive exposure periods, they may receive more than two bites on each arm during the test. A bite which is not followed by another bite in the same or the next exposure will be disregarded. If you are a treated subject you will still need to receive at least two more bites on that arm to reach breakdown. The untreated control subject will be exposed to stable flies every half hour for up to one minute in each of six test cages. Although we will try to brush the landing stable flies off before they bite, the control subject is likely to be bitten by some of them. We will minimize the irritation from bites or probes you receive by making Caladryl® or Calamine® lotion or rubbing alcohol available at the study site for your use after the study is completed.

**Reaction to the test repellents**

You may have a reaction to the test repellents.

The Sponsor has minimized this possibility by choosing an active ingredient (picaridin) that has demonstrated low oral, skin, and inhalation toxicity. The Environmental Protection Agency (EPA) has classified it as low toxicity for inhalation toxicity and primary skin irritation. EPA has classified the two test repellents as having low to mild toxicity based on eye irritation. For this reason it is important not to rub your eyes with your treated arms. The Sponsor has selected the non-repellent ingredients in the formulations because they are widely used in cosmetics and have a long history of safe use. ICR staff will be monitoring all subjects for any signs of a reaction to the test repellents. If you think you may be having such a reaction, tell a member of the staff immediately. A reaction may include redness, irritation, burning, swelling or a rash.

The stable flies being used in this study will be laboratory-reared and disease-free, and

Test subject's initials:.....

Date:.....

they will never have had a human blood meal. There is therefore no risk of your contracting any stable fly-borne disease as a result of participation in this study.

Should you have any medical problems, we will have First- Aid- qualified staff members and supplies on site. We will have cell phones to make emergency calls if necessary. In the case of medical emergency, we will transport you to a selected local hospital at our expense. We will pay all of your medical bills for study-related illnesses and injuries. The Principal Investigator will contact you by telephone, two weeks after the study to ask if you have experienced any adverse effects. You should contact the Principal Investigator any time after the study if you experience any study-related adverse effects, either before or after this follow up call.

**Financial Consideration**

We will pay you $11/hour for the first 9 hours and $17.50 for each additional hour that you spend on the day of the study. The study will last about 10 hours with an additional hour of prep time (11 hours total), with a total payment of $134. This payment will be mailed to you on the 15$^{th}$ or the last day of the month. If we ask you to drop out of the test, and you have complied with all of our requests, you will still receive full payment. If we ask you to drop out of the test because you have not followed all of our directions, or if you choose to drop out of the test, we will compensate you for time up to that point at the rate of $11 per hour.

**Costs**

There are no financial costs to you for participating in this study.

**Benefits**

You will get no personal benefit from participating in this study.
Some benefit may result for society in general through showing the effectiveness of these products in repelling a noxious pest.

Test subject's initials:.....

Date:.....

**Your Rights**

We will give you an opportunity to discuss with us any aspects of this document or of the study it describes that are not clear to you, so that you fully understand the nature of the study, its purpose, and the procedures to be used, as well as the discomforts, and risks you may experience during or after the study. You are encouraged to ask questions at any time, before or after you consent to participate, and before, during, or after the study day itself. Your participation is entirely voluntary. You may decide not to take part in this study, and if you decide you would like to participate, you are free to change your mind at any time without having to explain, and without penalty or loss of benefits to which you may be otherwise entitled.

**Alternative**

The only alternative is not to participate.

**New Information**

You will be informed verbally or in writing of any significant new findings discovered during the course of this study which may influence your continued participation.

**Voluntary Participation/Withdrawal**

You may be withdrawn from the study even if you want to continue. This could happen if (1) the study director believes it is in your best interest for you to stop being in the study, (2) or if you do not follow instructions for the study, (3) or if the sponsor stops the study for administrative or any other reasons.

**Questions**

If you have any questions about this study or suffer a reaction you think might be associated with the study, call us at 410-747-4500. If you have any questions about

Test subject's initials:.....

Date:.....

your rights as a research participant, or any related concerns or complaints, you may contact the Essex Institutional Review Board (IRB), 121 Main Street, Lebanon, NJ 08833, telephone 908-236-7735. The Essex IRB is a committee that has reviewed this research project to help ensure that the rights and welfare of the participants are protected and that the study is designed and carried out ethically. Review of this study by the Essex IRB is not an endorsement of the study or its outcome.

**Research Participation Information**

You can obtain information about participating in research studies from a number of sources.

A few are:

- Center for Information and Study on Clinical Research Participation (CISCRP): www.ciscrp.org
- Food and Drug Administration (FDA): www.fda.gov
- Office for Human Research Protections (OHRP)" www.hhs.gov/ohrp
- National Institute of Health: www.clinicaltrials.gov
- National Cancer Institute: www.nei.nih.gov
- Center Watch: www.centerwatch.com
- Various large university websites
- Various associations and societies concerned with specific diseases websites.

**Confidentiality**

We and the sponsor or its agents may use the information obtained from your taking part in this test, and this information may become part of a report. We will keep your participation as confidential as possible referring to you in the study data and reports only by your initials or an arbitrary ICR identification. However, we cannot guarantee that your identity will be kept confidential; the sponsor, personnel associated with the study, a regulatory agency such as the Environmental Protection Agency (EPA), and the Essex Institutional Review Board (EIRB) all have a right to review your records.

Test subject's initials:.....

Date:.....

**Consent**

I voluntarily agree to participate in this study. I will be given a copy of this signed form. By signing this form I have not given up any of my legal rights.

_____
Printed Name of Subject

_____
Signature of Subject Date

_____
Signature of Person Obtaining Consent Date

_____
Signature of Principal Investigator Date

Test subject's initials:.....

Date:.....

Stable Fly Repellent Test Recruitment Telephone Script
Protocol Number: G4330108001A382
Protocol Version Date: February 1, 2008
Subject Initials/#:

**ICR will be conducting a stable fly repellent study and a dose determination study for the this main repellent study on these dates, (Month, Day(s), Year). The location of these studies will be the ICR laboratory at 1330 Dillon Heights Avenue, Catonsville, Maryland. Will you be available on these dates?**

***If the person is available the inclusion/exclusion criteria will be discussed to verify whether the person qualifies to participate.***

**I will now read the inclusion criteria to you to see if you qualify to participate in the study.**

Inclusion Criteria:
**Please let me know if you do not satisfy any of the following inclusion criteria:**

**We will accept an equal number of male and female participants.**
**You must be between 18 and 70 years old.**
**There are no race restrictions.**
**You must be able to read, speak, and understand English.**
**You must consider yourself to be in good health.**
**For the repellent study only, you must be attractive to stable flies. We must verify this in the lab by inserting your untreated forearm into a cage of stable flies to see if at least 2 stable flies land within one minute.**

**I will now read the exclusion criteria to you to see if you do not qualify to participate in the study.**

Exclusion Criteria:
**Please let me know if you can satisfy the following exclusion criteria:**

**You cannot participate if you are pregnant or breastfeeding. All female subjects will be required to perform a urine OTC pregnancy test on the morning of the study.**

**You cannot participate if you are an employee or a relative of an employee of ICR Inc., the sponsor, toXcel, LLC, or any interested party.**

**For the repellency test only, you cannot participate if you are sensitive to stable fly bites.**

**You cannot participate if you have any known sensitivity to insect repellents or skin care products.**

*If an individual elects to participate in the study, after they have satisfied the inclusion/exclusion criteria, they must agree to the following:*

**I will now read a list of items that you must agree to in order to participate in the study. You must agree to follow the directions of the Principal Investigator and other ICR staff.**

**You must agree to abstain from the use of tobacco, alcohol, and all scented cosmetic products after 8 p.m. the night before the study, and on the day of the study until it is concluded.**

**For the repellent study only, you must agree to wear proper protective clothing such as blue jeans, heavy socks, long sleeve shirt, and gloves (gloves provided by ICR).**

*If an individual elects to participate in the study, after they have satisfied the inclusion/exclusion criteria and agree to follow the above we will then discuss the test with them.*

**STABLE FLY REPELLENT STUDY**

**You will be one of thirteen subjects who participate in this one-day laboratory study lasting about 11 hours. One of you will be selected by chance to serve as the "control subject", and will not be treated with the test repellents. The other 12 of you will be "treated subjects", and will be treated with both of the repellents, one on each forearm.**

**Every 30 minutes during the test, the untreated control subject will put one untreated forearm into each test cage containing 25 stable flies for one minute. If fewer than 2 stable flies land within one minute, these stable flies will be vacuumed from the cage and 25 more stable flies will be added to each cage to ensure enough activity for a valid test.**

**After the untreated control subject has verified adequate mosquito activity, the 12 treated subjects will carefully put both forearms into their assigned cage with the stable flies for five minutes.**

**This pattern will be continued every half hour until you receive either two stable fly bites on the same arm in the same 5-minute exposure period, or one bite in each of two consecutive 5-minute exposure periods, or until ten hours after your treatment, whichever happens first.**

**DOSE DETERMINATION STUDY**
**You will be one of twelve subjects who will participate in this one-day laboratory study**

**lasting probably less than 4 hours. Each of you will apply the two test repellents (a cream and a spray) three times to a marked out area of your forearm. We will measure the amount of repellent you and the other eleven subjects apply and average these amounts to determine how much repellent will be applied in the subsequent repellent study.**

***If an individual is still interested in participating in either study, we will discuss the ICD with them.***

**You are being asked to participate in a research study. Before agreeing to participate in this study, it is important that you read a form. This form is called an informed consent document. The informed consent document describes the purpose, procedures, benefits, financial payment, risks and discomforts of the study. It also describes the alternative procedures that are available to you and your right not to participate or to withdraw from the study at anytime. Please ask as many questions as you need to so that you can decide whether you want to be in the study. After reading this and having all questions answered, if you decide to participate, you should return this consent form to the to the study director. Sign the last page, initial and date each prior page in the presence of the study staff. You may refuse to participate in this study and this decision will not be held against you. If you are still interested in participating in the study we will mail an informed consent document to you for your review. In addition, after you have read the informed consent document, we would like you to come to the ICR office in person so that we can discuss the informed consent document with you and answer any questions that you may have. However if you are not able to visit our office prior to the study date, you must subsequently sign the ICD on the morning of the study at the ICR laboratory if you still wish to participate in the study.**

**Sponsor: LANXESS Corporation**
**Protocol #: G4330108001A382**

## STATEMENT OF COMPLIANCE
## (USA)

**Name of IRB:** **The Essex Institutional Review Board**
**Address:** **121 Main Street**
**Lebanon, NJ 08833**

The Essex Institutional Review Board is duly constituted (fulfilling FDA and OHRP requirements for diversity), allows only those IRB/IEC members who are independent of the investigator and sponsor of the trial to vote/provide opinion on the trial, has written procedures for initial and continuing review of clinical trials, prepares written minutes of convened meetings, and retains records pertaining to the review and approval process; all in compliance with the requirements defined in 21 CFR (Code of Federal Regulations) parts 50, 56 and 312, 45 CFR 46 and the International Conference on Harmonisation (ICH) guidance relating to Good Clinical Practice (GCP).

Glenn P. Lambert, MD
Signature of IRB Chairperson or Designee

February 5, 2008
Date of Signature

Glenn P. Lambert, MD, FAAP, Chairman
Printed Name

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**CHRONOLOGY OF EIRB APPROVAL THROUGH AMENDED SUBMISSION**

ICR | *Independent Laboratory*
*Pesticide Efficacy Testing*
*Regulatory Services*

Date: January 23, 2008

Chairman
Essex Institutional Review Board, Inc.
121 Main Street
Lebanon, NJ 08833-2162

**Protocol # G4330108001A382; ICR Project # 0108-433-0161**

Dear Dr. Lambert:

Please find enclosed our complete document package for your review and approval. The proposed date that the study will be sent to EPA/HSRB is **January 30, 2008**, so we respectfully request that we receive your approval prior to this date. We would like these documents sent to us by **Federal Express Overnight**, so please charge the delivery to our FedEx account number 1028-0348-5.

***We also request a copy of the minutes of the IRB meeting that pertain to this study, so that we submit them to EPA's HSRB as required by the Common Rule.***

We are enclosing the following documentation to support this request:

- -Protocol (2 copies) (please return **one approved copy** to us)
- -Informed Consent Form for the dose determination study (3 copies)
- -Informed Consent Form for the stable fly repellent study (3 copies)
- -MSDS' for each of the 2 test sample(s)
- -**Three** signed copies of the indemnification from LANXESS Corporation for Essex IRB (please return **two** signed copies to us)
- -**One** signed copy of the indemnification from LANXESS Corporation for ICR, Inc. (please keep for your files)
- -Memo re: ongoing training for investigators and staff in clinical research procedures
- -CV's for Charles Cornell, Gloria Stevens and Fouad Zgidou
- -CV's for the other ICR personnel participating in this study are on file at Essex IRB

will arrive under separate cover

Thank you for your attention, and please do not hesitate to contact me by telephone at 410-747-4500, by fax at 410-747-4928, or email address wgaynor@icrlab.com if you have any questions.

Sincerely,

William J. Gaynor
Principal Investigator

Enclosures



1330 Dillon Heights Avenue, Baltimore, MD 21228-1199 | **tel** 410.747.4500 | **fax** 410.747.4928 | **web** www.icrlab.com

**PROTOCOL NUMBER:** G4330108001A382


**PROJECT NUMBER:**
0108-433-0161

**PROTOCOL TITLE:**
**EVALUATION OF THE EFFICACY OF KBR 3023 (Picaridin; Icaridin)- BASED PERSONAL INSECT REPELLENTS (20% CREAM and 20% SPRAY) AGAINST STABLE FLIES IN THE LABORATORY**

**PROTOCOL VERSION DATE**
January 21, 2008

**PROPOSED LABORATORY INITIATION DATE**

TBD
**PROPOSED LABORATORY CONDUCT COMPLETION DATE**
TBD

**STUDY DIRECTOR**
William J. Gaynor

**STUDY ASSOCIATES**
Charles Cornell, Timothy Foard, Niketas Spero, Gloria Stevens and Fouad Zgidou

**SPONSOR REPRESENTATIVE**
**G.K. Sangha**

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

**TESTING FACILITY**
ICR, Inc.
1330 Dillon Heights Avenue
Baltimore, MD 21228-1199

## TABLE OF CONTENTS

# EVALUATION OF THE EFFICACY OF KBR 3023 (Picaridin; Icaridin)- BASED PERSONAL INSECT REPELLENTS (20% CREAM and 20% SPRAY) AGAINST STABLE FLIES IN THE LABORATORY

## 1. INTRODUCTION

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 for safety, low skin penetration, 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). LANXESS is the study sponsor.

Icaridin (US EPA registration name Picaridin), the current common name, was developed under the Code Name KBR 3023 and the registered trade name 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. Despite this, Picaridin and KBR 3023 will be used henceforth as these names have become the most widely used ones in the U.S.

## 2. OBJECTIVE OF THE STUDY

The objective of the study is to determine the mean protection time from bites by stable flies provided by the test articles under laboratory conditions to confirm this hypothesis.

## 3. HYPOTHESIS

Two repellent products (205 formulations of All-Family Insect Repellent Spray and All-Family Insect Repellent Cream and referred to as "test articles" and "test products' henceforth) are expected to provide 8 hours or greater than 8 hours of personal protection from stable flies (also referred to as "flies") in a laboratory test. (also referred to as "study").

## 4. STUDY RATIONALE

ICR Inc. ("ICR"), located at 1330 Dillon Heights Avenue, Baltimore MD 21228-1199, will conduct the proposed test at its laboratory. This will evaluate the efficacy of two 20% KBR 3023-based insect repellent products (KBR 3023 All-Family Insect Repellent Spray and KBR 3023 All-Family Insect Repellent Cream) against laboratory-raised stable flies. Laboratory studies, such as the one proposed, have been considered by regulatory authorities and the scientific community to be a reliable method for testing the performance of topically-applied insect repellent products. Under EPA's OPPTS Guideline 810.3700 ("Product Performance of Skin-Applied Repellents of Insect and Other Arthropods") human efficacy study data is required to support registration of insect repellent products to substantiate the product label claims.

The products (20% Formulations of All-family Insect Repellent Spray and All-Family Insect Repellent Cream) are conditionally registered by EPA pending conduct of new efficacy data including stable flies. However, no testing of 20% KBR 3023 products has been conducted against biting flies in the US or Europe. A 7.5% KBR-3023 is the highest level tested in a field and a cage study conducted in Europe, but it involved three species which do not occur in the U.S., as well as stable flies, (unpublished LANXESS study 06-LX-04, 2007). The study duration was limited to only four hours and the details of the data are not available. Therefore, this study is planned to determine the efficacy of the two 20% KBR 3023 products in a cage test.

Stable flies can transmit animal-related diseases, but very rarely transmit any diseases which afflict people. The pest status of these flies as they relate directly to humans is almost entirely due to their painful bite and annoyance. They are rapid fliers and easily elude the swatting hand or rolled newspaper. The data generated from the study will provide consumers with an alternative and effective choice of a repellent.

## 5. RISKS AND BENEFITS

The main risks associated with the proposed study are the potential for allergic or irritation responses to the test materials, and exposure to biting flies. The potential for disease transmission is almost non-existent. Risk to the subjects health and safety are not likely either during or after the study as described below:

Most people do not exhibit a skin reaction to stable fly bites other than feeling transient pain. ICR's stable flies have been raised in the laboratory for many generations and have not been exposed to human blood sources (they are fed *in vitro* on bovine blood). Therefore the potential risk of contracting an insect-borne disease will be essentially zero, leaving irritation from stable fly bites as the only hazard from these insects.

Picaridin has low acute toxicity and long term studies showed no adverse effects of concern by the use of the product. The product has been registered in 33 countries and over years of use showed that it can be used safely (the safety profile of the product, as provide by the sponsor, is presented in Appendix V). The 20% concentration of the active ingredient in the two All-family formulations proposed for the study is higher than the marketed and EPA-registered formulation. The product will be used according to current label and risks associated with the use during the study are not anticipated.

The inert ingredients used in the two products have been used extensively in the cosmetic industry without adverse events. Subjects with a history of reaction to insect bites, insect repellents, and skin care products will be excluded from the study. Further, the subjects will be closely monitored during both the dose-determination phase of the study, as well as during the repellent phase of the study, for signs of reactions. Subjects will be especially closely monitored during the dose-determination study when they apply the products to their forearms (see *Dose Determination*). Prompt medical attention will be sought should any adverse reaction be experienced.

## 6. STUDY OVERVIEW

There will be two phases of the study: the dose determining phase and repellent phase.

*a) Dose Determination Phase*
The test doses will be determined before the repellent test by allowing human subjects to apply both products to their forearms. These subjects will be instructed to apply the products as they would normally when applying a repellent, the only criterion being that the amount applied is what they would choose. ICR will measure the weights applied. Each subject will apply each product three times. The means of these application weights will be used to treat the subjects in the repellent test. This is detailed below under section 11 (page 17)

b) *Repellent Test Phase*
ICR plans to test 12 human subjects, with their left forearms treated with the cream product and their right forearms with the spray products, for repellency to groups of 25 caged stable flies. Subjects will expose their treated forearms to these flies for 5 minutes every half hour for 10 hours, or until they receive a confirmed bite on both arms, whichever occurs first. The times to the first confirmed bite will be the protection time for each product on each subject. Ten hours will allow a reliable documentation of an 8-hour claim. This phase is detailed below under section 20 (page 22).

## 7. TEST ARTICLE (PRODUCT) NOMENCLATURE, INFORMATION AND DISPOSITION

a) *The table below summarizes the identity of the two test articles.*

| Active Ingredient | Product Name | EPA Reg. No. | Application Rate | ICR Code |
|---|---|---|---|---|
| **20% Picaridin*** | **KBR 3023 All-Family Insect Repellent Cream** | **39967-50** | ≤4 mg/cm$^{2*}$ ≤1000 mg/250cm$^{2*}$ | **A** |
| **20% Picaridin*** | **KBR 3023 All-Family Insect Repellent Spray** | **39967-53** | ≤4 mg/cm$^{2*}$ ≤1000 mg/250cm$^{2}$ | **B** |

* 2-(2-hydroxyethyl)-1piperidinecarboxylic acid 1-methylpropyl ester

b) Upper limit for treatment dose
The amount to be applied will be determined in the dose determination phase of the study, but in no case will it exceed 4 mg/cm$^2$ without additional review and approval by EIRB as this is the maximum application rate that they will be provided for the purpose of hazard assessment.

c) MSDS
A Material Safety Data Sheet (MSDS) shall be provided for each test, control, and/or reference sample, which will include any hazardous information of the test articles. The percentage of all active ingredients and any hazardous constituents must be included in all MSDSs.

d) *Chain of custody letter*
A chain of custody letter must accompany all test, control, and/or reference test articles.

- **e)** *Test Article Characterization*
  Sample characterization is a key GLP (Good Laboratory Practices) requirement detailed in 40 CFR Part 160. The sponsor is solely responsible for conducting the complete test article, control sample, and any reference sample characterizations according to GLPs, and for providing ICR with this characterization data prior to the experimental start date of this study. This characterization must define the identity, strength, purity, and composition of the batch(es) or lot(s) of test articles. If any of the test, control and/or reference test articles are currently available for consumer use and/or purchased in the marketplace, ICR will need the same characterization information provided by the sponsor prior to the experimental start date of this study. If documentation of this characterization is not provided prior to the experimental start date, this will be noted as a non-compliance item in the GLP compliance statement. This sample characterization

information will be retained in the ICR archives, and a statement identifying this location will be included in the final report. LANXESS has agreed to provide this information.

f) *Sponsor Responsibilities*
The study sponsor shall provide the study director with the entire compositions of the test articles prior to the experimental start date.
The stability of the test and, when applicable, control, and/or reference test articles shall be determined by the sponsor prior to the experimental start date. When relevant to the conduct of this study, the solubility of each test, control, and/or reference sample shall be determined prior to the experimental start date.

Methods of synthesis, fabrication, or derivation of the test, control, and/or reference test articles shall be documented by the sponsor, and the location of such documentation shall be specified by the sponsor in a letter to the Study director. LANXESS has done this.

The stability of test, control, and/or reference test articles stored under the test site conditions shall be known for all studies. LANXESS has this information.

g). *Return of Unused Test Articles*
All unused portions of the test articles will be returned to the sponsor within 30 days of the final report being sent to the sponsor. The sponsor will be responsible for all costs for the return of the test articles, including any costs associated with hazardous materials shipping.

## 8. TEST ORGANISM

*a) Introduction*
The stable fly (*Stomoxys calcitrans* L) resembles the better known house fly (*Musca domestica* L.). Close inspection reveals that it has the piercing mouthparts (proboscis) of a blood-feeder rather than the enlarged, rounded tip of the house fly's mouth parts (which is used for swabbing up food). Stable flies are obligate blood feeders with both sexes relying upon this diet (unlike mosquitoes in which only the females will take blood meals). Stable flies attack cattle, horses and other farm animals, household pets and people. Their bite is painful, often more so than that of a mosquito. The itching and swelling which often follows a mosquito bite, is however, usually lacking after stable fly bites. They are restless biters and will often interrupt a meal to fly elsewhere. As noted below stable flies rarely, if ever, transmit diseases to humans but they have been implicated in diseases to animals (e.g. anthrax and the equine nematode parasites of the genus *Habronema).*

*b) Origin of ICR Stable Fly Colony*

The source of ICR's stable fly colony is the colony maintained by USDA Gainesville, Florida. Pupae from this colony were obtained in November 2006. Prior to this ICR had maintained a stable fly colony originating from USDA Kerrville Texas in 1983.

c) Stable Flies for Repellent Study

Groups of twenty-five adult, mixed sex, 3-10 day old stable flies will be aspirated from stock cages and released into each cage for each 5- minute exposure period. These test stable flies will have been fed 10% sucrose rather than their normal diet of citrated bovine blood. They will have had no sucrose for twenty-four hours prior to the study and they will have not have received a blood meal.

## 9. TEST CAGES

a) *Description*

There will be six test cages and two subjects will use each cage. The aluminum test cages (constructed by ICR) measure 2 x 2 x 2 feet with two sleeved entry ports on each of two opposite sides of the cage (4 entry ports/cage). The cage sides (except for the sleeved entrances) and top are screened. The floor is lined with a reflective material to facilitate observation of stable flies landing on the under surfaces of the forearms. A bar runs across the center of the cage to serve as a hand rest. See figures 1 and 2 below.

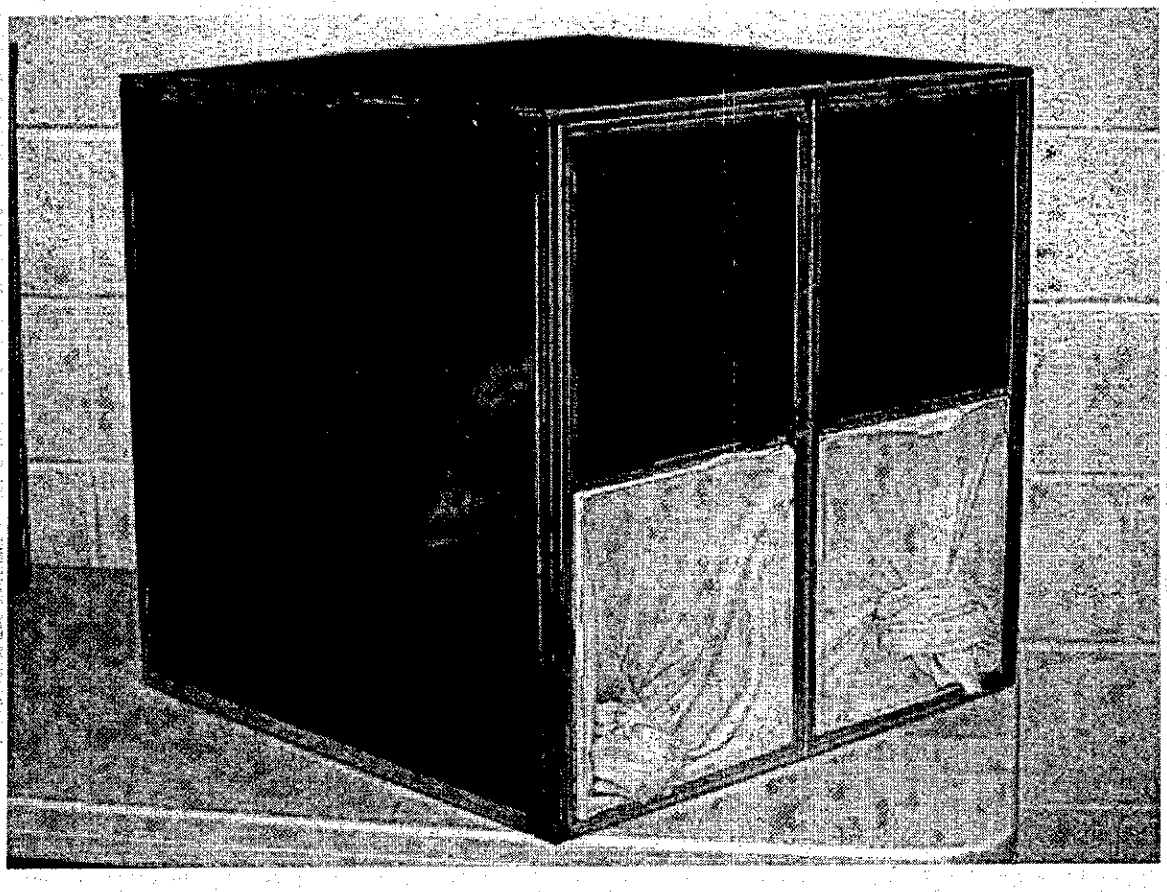


Figure 1. Test cages showing entrance sleeves closed

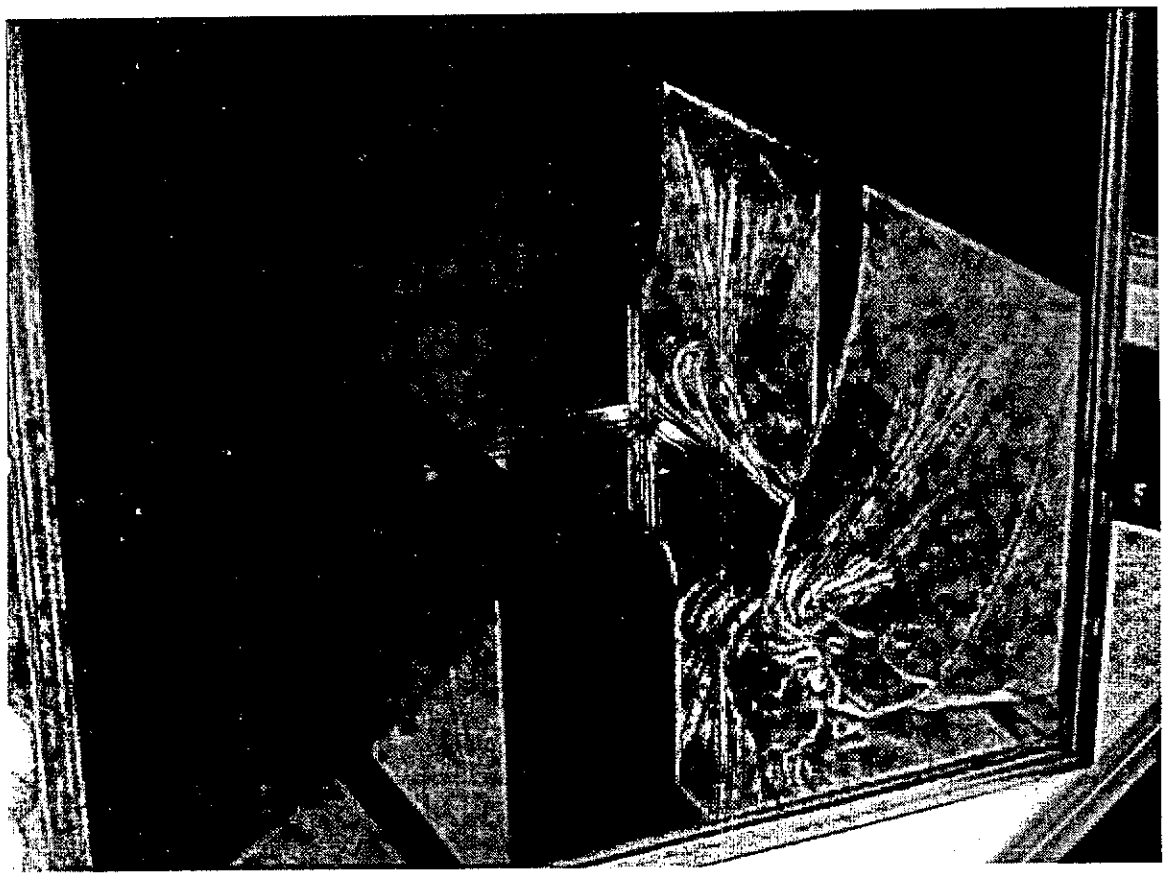


Figure 2. Test cages show hand rest bar and reflecting mirror.

*b) Evidence for Lack of Interference between Two Subjects' treated Forearms in Cages*
ICR has tested pairs of subjects in these cages with mosquitoes or stable flies for over 30 years and has not seen any evidence of interference between different treatments. Evidence of this lack of effect is provided by incomplete treatments or abrasion of treated forearms. In the former, if a 250 $cm^2$ area of a forearm is incompletely treated such that areas of skin are left untreated, stable flies will promptly land on these areas, despite the close proximity of treated skin. Similarly, ICR has seen cases where subjects have accidentally rubbed their treated forearms against their sides or another object, removing some of the product. Stable flies will often land on these abraded areas before the nearby unabraded areas.

## 10. USE OF HUMAN SUBJECTS

### a) Introduction

There are currently no viable alternatives to using human subjects to determine the efficacy of insect repellents. Under the Federal Insecticide, Fungicide and Rodenticide Act ("FIFRA"), EPA requires that efficacy data collected from human studies be submitted to register for insect repellents. These data must substantiate any public health protection claims made on the product's labeling. Specifically, data are required to both substantiate the repellency of specific insect pests and inform the user how long the products will repel the pests on the label.

While there is an economic incentive to the sponsor of the study to offer a new insect repellent alternative to consumers, such products must benefit consumers or these products will not be purchased or used. It is important to bring new insect repellent products to market so that consumers have alternatives that are effective, acceptable and convenient to use. The products to be tested in this study have been formulated to provide protection from stable flies and to be easy to apply, pleasant to use and offer alternatives to those containing other repellent active ingredients, such as DEET.

ICR will evaluate repellency based on protection from bites while conducting laboratory studies to try to minimize discomfort to the test subjects. Efficacy is defined as the Protection Time (PT). The PT is the time interval between the application of the repellent and the First Confirmed bite (FCB). A stable fly inserts its proboscis into the subjects' skin – an act which is both felt by the subject and observed by an ICR staffer. The FCB is a bite which is followed by another bite within 30 minutes.

This study is intended for submission to EPA to support an insect repellent label claim for stable flies. The results obtained from the study will enable the product to be used worldwide if repellency is demonstrated.

### b) Justification for use of human subjects

Human subjects are required for this study because there are no satisfactory substitute models for testing insect repellents. EPA recognizes this in its draft OPPTS Guideline 810.3700 which require testing of repellents on human subjects. While there has been experimental work on product repellency using animal models, such as mice and guinea pigs, the data are not a sufficiently reliable predictor of performance on humans.
It needs to be noted that animal testing has its own set of ethical concerns, including the impossibility of obtaining informed consent from the animal subjects.

**c) Recruiting pool**

ICR is located in Baltimore County, Maryland. According to the 2000 Census, the racial makeup of Baltimore County 74.39% white, 20.10% black or Afro-American, 0.25% Native American, 3.17% Asian, 0.03% Pacific Islander, 0.62% from other races, and 1.43% from two or more races.

**d) ICR's Pool of Candidate Subjects and Plans for Representative ness**

ICR's current pool of potential subjects are all white. Afro-Americans and North Africans have participated in previous studies. For the proposed stable fly test, ICR will look for recruits from the Afro-American community, as well as from the white majority population to correct this slight imbalance.

**e) Selection Criteria**

*Inclusion Criteria:*

| | |
|---|---|
| Number: | 12 test subjects and one negative control subject needed |
| Sex: | Male or Female |
| Age: | 18 to 70 |
| Race: | No exclusions |
| Literacy: | Must be able to read, speak, and understand English |

*Exclusion Criteria*:

1. Test subjects can not participate if they are pregnant or breastfeeding.
2. Test subjects can not be an employee or a relative of an employee of ICR Inc., the sponsor, or any other interested party.
3. Test subjects must follow the requirements of the study as explained to them.
4. Test subjects must not be known to be unduly sensitive to stable fly bites (this is not an exclusion from the dose determination phase of the study)
5. Test subjects must have no known sensitivity to insect repellents or skin care products.
6. Test subjects must be attractive to stable flies, as evidenced by previously being bitten by stable flies (optional for dose determination)
7. Test subjects must not smoke or drink alcoholic beverages 12 hours prior to the test.
8. Test subjects must not use perfumed cosmetics, skin creams, shaving lotions, etc. after 8 P.M. the night before the test, and during the test.

ICR complies with the EPA's Final Rule governing the use of human test subjects, and adheres to 40 C.F.R. Part 26 Subparts K and L when it uses human subjects in studies.

**f) Institutional Review Board**

All EIRB documents will be submitted to EPA/HSRB as a package separate from the protocol. ICR uses the following institutional review board ("IRB"):
Essex Institutional Review Board, Inc. ("EIRB")
121 Main Street
Lebanon, NJ 08833

This IRB is accredited by PHRP (Partnership for Human Research Protection Inc.), and is currently in the process of obtaining accreditation from AAHRPP (Association for the Accreditation of Human Research Protection Programs).

Approval of all documentation for human subject testing must be obtained from EIRB, EPA, and the HSRB before such testing can occur.

**g) ICR's Use of Selection Criteria**

ICR has developed a pool of male and female test subjects. The test subjects ICR recruits represent a diverse group including retired teachers, business owners, contractors, engineers, as well as students, homemakers and others.

ICR will exclude pregnant and breast feeding women from this study due to ethical concerns. ICR will also exclude children under the age of 18 for the same reason. Individuals unable to read, speak, or understand English will be excluded to ensure that all test subjects understand the ICD and test parameters. Employees or relatives of employees of either ICR, the sponsor, or other interested parties, will be excluded to avoid the possibility of coercion. Individuals sensitive to stable fly bites, insect repellents, or skin care products will be excluded to avoid placing them at risk. Although these groups of people that ICR would exclude are groups of people who would probably use repellents, their exclusion is justified because this will protect them from potential hazard.

ICR's list of potential test subjects is as representative of potential repellent users as ICR is able to make it in terms of both practical and ethical considerations. ICR test subjects need to be in good health to withstand the rigors of the specific test. In the case of this laboratory test, the rigors will be very minor – boredom is likely to the main one. ICR will accept individuals between the ages of 18 and 70. This age group represents a large portion of the US population who would encounter stable flies and have a need to use insect repellents. Since there is no risk of arthropod-borne disease, exclusion of individuals over 55 is not justified.

ICR will select individuals from its database of candidate test subjects. This will be accomplished by drawing numbers that correspond to the candidate subjects. ICR will attempt to select even numbers of male and female test subject (6 female and 6 male in this test) to

eliminate any gender bias in this test. The reason for this is that gender has been shown to affect attractiveness of the subjects to mosquitoes and the same may be true of stable flies.

**h) Consenting**

All candidates will review and sign an Informed Consent Document ("ICD") prior to acceptance as study subjects. The ICD will be formally explained to all candidates before the study is scheduled to begin. A candidate may visit ICR to review and sign the ICD or the ICD can be mailed to the candidate for their review. If mailed, the study director will phone the candidate to answer any questions regarding the ICD. If any candidate refuses to sign after learning the details of the document, they will not be allowed to participate in the study. After the ICD is fully described to the candidate, he or she may then sign the ICD in the presence of an ICR staff and a copy of the ICD will be made and returned to the candidate. He or she will then be notified within one week if they have been enrolled as a subject in the study. The Informed Consent Document will have been approved by an Institutional Review Board before it is presented to the candidates for the study.

**i) Remuneration**

For the dose determination part of the study, the subjects will be paid $11/hour for a 9 hour day even though the duration of this part of the study is likely to be less than 4 hours per subject.

For the repellent part of the study, the subjects will be paid $11/hour for the first 9 hours and $17.50 for each additional hour they spend on the day of the study. The study will last about 10 hours with approximately one hour of preparation time for a total of 11 hours. A total payment of $134 will be paid to each test subject for the day. If a subject drops out of the test at our request but they have complied with all of our requests, they will receive full payment. If the subject drops out of the test either at our request because they have not followed all of our directions, or they just choose to drop out, they will be compensated for their time up to that point at the rate of $11 per hour.

Payments will be mailed to the subjects on the 15$^{th}$ or 30$^{th}$ of the month.

**j) Recruitment Procedures**

ICR has been conducting repellent studies for over thirty years. During this time ICR has amassed a large list of potential subjects. Some of these subjects refer friends and colleagues to ICR. When a repellent study is planned, ICR will contact candidate subjects in its data base by telephone and briefly discuss the study. Any study specific inclusion/exclusion requirements will also be mentioned at this time.

ICR will use the following initial telephone script to recruit test subjects for this study:

## 11. DOSE DETERMINATION

### a) Introduction

The label directions on insect repellents provide general instructions on how much product to apply, but consumers may ignore these instructions or the instructions may be too vague to instruct the consumer adequately. The proposed study will include a dose determination phase before the repellent test is conducted. This will allow the products to be tested at rates which consumers are likely to use. Therefore 12 subjects will be recruited, as described above, to determine typical consumer doses for both products.

### b) Preparation of Subjects

ICR staff will measure the subjects' forearms and demarcate 250 $cm^2$ areas for treatment, as described subsequently, under *Personnel Preparation.*

### c) Separation of Subjects

It is important that subjects are not able to observe or converse with each other before or during application of the products as this could bias them as to how much they would apply. Therefore each subject will move to a separate room with an ICR staff member present before treatments begin.

### d) Applications of Cream Product

The subjects will be given a copy of the label for the cream product and a sample of the cream. They will be asked to apply the cream, according to label directions, to their forearm, using their gloved hand, until they have applied what, in their opinion, is enough. The weight of product applied will be calculated by weighing the product container before and after application. Subjects will then wash off the cream using soap and hot water, dry their arms and repeat the process for a total of three applications.

### e) Applications of Spray Product

The subjects will then be given a copy of the label for the spray product and a sample of the product itself. They will treat their forearms with the spray. They need to be able feel the spray hitting their skin in order to decide when enough has been applied, but some of the spray droplets will blow by their forearms, making accurate measurement of the dose applied difficult. Therefore a different method is called for. An approximately 5 cm wide band of water proof surgical dressing will be wrapped around the central part of each forearm with the impervious layer against the skin and secured by two rubber bands. A layer of gauze, or other absorbent material, will be wrapped around the dressing to provide additional absorbent capacity. The subjects will then spray their forearms until satisfied that enough has been applied. The dressing, gauze and rubber bands will be weighed before and after to determine the weight applied per unit area and converted to the weight to be applied per 250 $cm^2$. This procedure will be repeated for a total of three applications.

"ICR will be conducting a repellent project on (date) at ICR. Would you be interested in participating?"

If the candidate is interested and is available, the inclusion/exclusion criteria will be discussed in more detail to determine if they qualify to participate. The ICD will also be discussed with them at this time. In addition, ICR will mail a copy of the ICD to each candidate for their review. They will be instructed to contact the study director to verify receipt of the ICD and to ask any ICD or study-related questions they may have.

The study director will contact all candidate subjects by phone several days after their receipt of the ICD to make sure that all their questions have been answered. All candidates will be offered the opportunity to come to ICR to go through the consent process in person. If contacted individuals choose to visit ICR office, they may voluntarily sign the ICD if they wish to be enrolled in the study. If they choose not to visit ICR's office prior to the study date, they must sign the ICD on the study day before taking part in the study.

Any candidate who declines to sign the ICD will not be permitted to participate in the study.

There will be no coercion for any candidate to participate. The inclusion/exclusion criteria are clear, the payment is simple; the candidates will be informed of the conditions they will likely encounter and what is expected of them.

Each female candidate will be informed that if they sign the ICD and want to participate in the test, they will be required to perform an over the counter pregnancy test on the morning of the study. The test results will be confirmed by a female ICR employee and the study director. Once they have signed the ICD, each consenting test subject will be informed that they may drop out of the study at any time without penalty (except that they will lose some of their potential remuneration, based on the time they miss). Further, they may leave as soon as practical after early withdrawal from the test.

**k) Pregnancy Testing**

After signing the ICD and shortly before any treatment with a test articles, each female candidate will take a pregnancy test as described by the label of an over-the-counter pregnancy test kit supplied by ICR. This will apply to the dose determination phase (section 11 below) and to the repellent test phase (section 20 below). Any subject who shows a positive result will be discretely excluded from further participation. The presence of multiple female subjects will allow the reason for their exclusion to be kept private. A female ICR staff member will confirm the pregnancy test results. The study director will be advised of the results, but no one else will be. The reason for the positive subject's exclusion from the study will be kept private by the study director informing the other subjects that this subject has not been able to meet one of the inclusion or exclusion criteria, without specifying which one.

**f) Calculation of Dose**

The weights of the cream and the spray product will be averaged per subjects (mean of three applications per product). Then an overall mean will be calculated for all subjects for each product. These overall means will be the doses to be used in the repellent test with stable flies. The standard deviation and standard error of the mean will be calculated for each product across all subjects to determine the spread of application rates in this small sample of the general population.

## 12. NEGATIVE CONTROL

One subject will be selected to be the negative control. Selection will be by a drawing of numbers. One untreated arm of the control subject will be used to establish the aggressiveness of each cage of 25 stable flies.

Twenty five stable flies will be added to each cage at the start of test. The control subject will insert his/her untreated forearm into each cage and leave it there until two stable fly landings have occurred. An ICR staffer will gently push landing flies off the control subject's arm before they can bite by reaching in with a protected hand from a port on the other side of the cage with a wooden applicator stick. This approach will be needed since stable flies, unlike mosquitoes, can cling too tightly to a subject's arm to be easily shaken off. ICR staff will record the time when two landings occur.

If fewer than two stable flies land in 60 seconds in any of the six test cages, all stable flies will be vacuumed from all six cages and a new group of twenty-five stable flies will be released into all six cages.

No comparison will be made between the control landing rate and the treated subjects.

## 13. RATIONALE FOR NOT HAVING POSITIVE CONTROLS

Firstly, EPA is not requiring positive controls. Secondly, sufficient biting pressure (as evidenced by at least two landings in 60 seconds in a 250 $cm^2$ area on an exposed untreated control arm) will be confirmed at the start and throughout the study before each exposure period. Thirdly, a positive control group would not confirm the stable fly repellency of the test product nor would it help in determining a reliable protection period for these products under laboratory conditions. Finally, putting additional subjects at risk, however minimal, would be unethical

## 14. SUPPORT STAFF

Additional ICR staff members will support the study director and test subjects in their activities These ICR staff members, along with the study director, will record all test data. Test subjects will not record any data. ICR staff are trained in the procedures to be used in this test and are familiar with ICR's SOPs. The quality of the study results could suffer and these results would be difficult to defend in one of the routine an EPA audits which ICR is subject to. The same difficulty would apply to a court of law if untrained test subjects recorded data.

## 15. MISCELLANEOUS SUPPLIES

Syringe, (minus the needle), micropipette and tips, Q-tip®s, latex or vinyl gloves, clip boards, data record forms, scissors, elastic bandages, water proof surgical dressing, gauze, rubber bands, Elastikon® tape, pencils, marking pens (e.g. Sharpie®), hygrothermograph, unscented Neutrogena® soap, paper towels and a stop watch, Caladryl® or Calamine® lotion.

## 16. RECORDS TO BE MAINTAINED

All study notes, data collection sheets (true copies), SOPs (originals), Chain of Custody letters (true copies), Sample Log and Sample Record of Use Forms (true copies), the protocol (true copy) and signed Informed Consent documents will be maintained in the ICR archives. Original documents will be provided to the sponsor for archiving with the exception of SOPs, Master Schedules, signed Informed Consent documents, test article characterization, and personnel files.

## RISK CHARACTERIZATION AND MINIMIZATION

The subjects will be exposed to two types of risk:

1. *Test products.*

These proposed insect repellents use the active ingredient, Picaridin, which was registered by the US EPA under FIFRA on December 7, 2000. As required under FIFRA, registration of Picaridin is supported by an extensive data package that includes toxicity test data that demonstrate low acute and chronic toxicity. The EPA "New Pesticide Fact Sheet" for Picaridin indicates that its toxicology data base is complete and no additional studies are required. This active ingredient has been used without significant incident by the study sponsor and other insect repellent companies and many consumers. All of the inert ingredients used in the finished insect repellent products have a long history of safe use in various cosmetics.

For registered products containing Picaridin®, the EPA risk assessment assumes that each application of insect repellent products is to a skin surface area of 4,538 $cm^2$ for adults. In the proposed test, the product will be applied once to the subjects on the test day over a surface area of only 500 $cm^2$ (*i.e.* 250 $cm^2$ on each forearm). Consequently, the test subjects in this study will only be exposed over an area of approximately 11 percent of that previously reviewed and approved by EPA for products with the same Picaridin® concentration. Further, the label directions of these registered products allow for up to two applications per day, while the efficacy study will employ only one (however the dose determination study will involve three or occasionally, four applications). A 100-fold margin of exposure (MOE) is considered to be the target for the determination of acceptable risk from systemic exposure. The MOE is based on the No Observed Adverse Effect Level (NOAEL) for systemic effects, the concentration of active ingredient in the formulation, frequency and rate of application, skin surface area and body weight, and dermal absorption. The MOE for the test subjects in this efficacy study will substantially exceed the minimum 100-fold target and is, therefore, considered acceptable under widely recognized scientific standards.

While there is little concern for the test articles to induce an adverse reaction in the test subjects, they will be monitored throughout the study and prompt medical attention will be obtained if any adverse reaction is observed among the subjects in the test. Those individuals who are known to have allergies to stable fly bites, insect repellents, or skin care products will be excluded from the study.

2. *Bites from stable flies.*

The principal effect of a stable fly bite is a sharp but transient pain. In most cases, stable fly bites do not lead to the itching and localized swelling which are the typical aftermath of mosquito bites. A few people may experience a small area of redness, swelling and itching that usually goes away within 24 hours. In extremely rare cases, a serious reaction to a bite may result in swelling of the throat, hives and wheezing. This condition (anaphylaxis) could be life-threatening and requires immediate medical attention. All subjects known to have severe reactions to stable fly bites will be excluded from this study.

All subjects will wear latex or vinyl gloves. Only a small portion (250 $cm^{2)}$ of bare skin on each arm will be exposed. All other parts of the body will be covered with the subject's personal clothing. This will protect them in case of any escaped flies. Immediately upon receiving a FCB on an arm, that arm will be withdrawn from the test and not be exposed to the caged stable flies again. Caladryl® or Calamine® lotion and rubbing alcohol will be available for use to mitigate any reaction to stable fly bites.

An ICR staffer trained in First Aid will be on site, and First Aid supplies will be available. A selected local hospital will receive prior notification of this study and on-site staff will have cell phones to make emergency calls if necessary. In the case of medical emergency, people will be

transported to the selected local hospital, St. Agnes Hospital, by either ICR staff or ambulance. The hospital is 7 miles from ICR, at 900 S. Caton Ave., Baltimore, MD. 21229. The telephone number of the ER center is 410-368-2000. If any test subjects need medical attention, their medical care will be paid by ICR.

*Arthropod-borne diseases*

As noted previously, there will be no risk for arthropod-borne diseases from the stable flies used in this study. Stable flies are known to carry human diseases only very rarely, if at all. More importantly, this strain has been reared in the laboratory for many years and has not been allowed to feed on human blood (bovine blood is used). Owing to the forgoing factors, transmission of a blood-borne disease by these stable flies is not possible.

Finally, the subjects will only need to receive two bites within 30 minutes to confirm breakdown, after which the test arm will not exposed to flies again, thus minimizing their exposure to the flies.

## 19. DISCOMFORT AND HAZARD (EIRB Mandated Section)

The stable flies being used in this test are not capable of transmitting diseases in the wild. This strain of stable fly has been laboratory colonized for many years and has not been exposed to outside blood sources while at ICR. None of the stable flies used in this test will have had a blood meal prior to their introduction into the test cages. Once a group of stable flies has been used in a study, it will not be re-used in another study. All stable flies used in the study will be destroyed either through freezing or carbon dioxide. Transmission of a blood-borne disease by this strain of stable fly is not possible.

In the event that study related injury or illness should occur, test subjects would be instructed to seek medical attention through a health care provider, at ICR's expense. Test subjects would be instructed to submit study related bills to ICR for payment ICR will incur the cost of any such study-related bills. The study director will contact all test subjects by telephone, two weeks after the conclusion of the study, to enquire if they have experienced any adverse effects.

## 20. BENEFITS

The sponsor will gain the most benefit from this study through knowledge gained on the performance of its repellent products. Indirect benefit may accrue to society at large by the development of more effective, safer and 'pleasant-to-use' repellent products, and alternatives to DEET-based products.

## 21. REPELLENT TEST METHODS

**a) Experimental Design**

The purpose of this study is to determine the extent to which a stable fly repellent is effective in preventing bites on exposed human skin. The repellent will be considered degraded if either of these two conditions is met: a) two stable fly bites are noticed in a single 5 minute observation period; or, b) a single bite in two adjacent observation periods is noted. The goal of the study is to provide an estimated length of protection time that a specific repellent provides.

Individuals will have repellent applied to a specific area of their forearms. Then, their arms will be exposed to live stable flies for five minutes. If two bites are noted in this time period, the case will be considered a "bite". If no bites are noted, the arm will be removed and re-exposed 30 minutes later for another 5 minutes. This process will continue either till two bites are noted or 10 hours have elapsed. The 250 $cm^2$ delineated areas on the arms of subjects will be treated and used as test areas. Only arms are being treated in this study, since arms are easy to monitor for stable fly activity. Therefore there will be twelve test arms for each treatment. Each test subject will have one arm treated with the cream product and the other arm will be treated with the spray product. ICR staff will know the identity of the treatments, but the test subject will not.

**b) Rationale for Sample Size : Number of Subjects**

The EPA draft Guideline OPPTS 810.3700) currently (1/2008) on EPA's website recommends 10 test subjects to document a protection time greater than 5 hours. Because of the high cost of doing repellent studies and the need to avoid unnecessary exposure to subjects, it is prudent to ensure data is collected from the minimum acceptable number of subjects. Therefore the target number of test subjects in the study is twelve, which includes two additional subjects in case of drop outs or ones failing to meet an exclusion or inclusion criterion on the day of the test. There will also be one negative control subject.

The choice of 12 subjects is discussed further in DATA ANALYSIS (section 23).

**c) Test location:**

This test will be conducted in the laboratory at ICR. The laboratory is maintained at ambient relative humidity and 70° F ± 15°F. These are the same conditions as the stable flies are reared under so their activity should be unimpaired; there is no need for elevated humidity as is the case with mosquitoes.

**d) Dose**

The dose will have been determined from the dose determination part of the study conducted prior to the beginning of the repellent test (see *Dose Determination* above). This dose must be

no greater than 4 mg/cm$^2$. If it is greater, an additional approval will be needed from EIRB before the repellent test can take place, since 4 mg/cm$^2$ has been given to ERIB as the upper limit for their evaluation.

**e) Blinding of the Study**

The test articles will be coded as "A" (cream) and "B" (spray). During the test these codes will be the only test article designation referred to or that the test subjects will see. The study director and members of the ICR staff will know the actual test articles, but will refrain from such identifications in the presence of test subjects. It should be noted however that the different appearance and texture of the cream and the spray will probably be apparent to the subjects.

**f) Treatment Groups and Subject Selection**

There will be two groups: a treated group of twelve (two more than required to allow for drop outs) subjects whose arms will be treated, and one untreated (control) subject whose arms will be untreated. Subjects will be given a subject number. They will be assigned to the groups by lottery selection of the subject number.

**g) Personnel preparation**

All subjects will have reviewed and signed an ICD before acceptance as a test subject participant.

i) *Pregnancy Testing*

All female subjects will conduct a urine pregnancy test on the morning of the test before any treatments. This procedure was described under section 10k.

All test subjects will then wash their arms with unscented Neutrogena® soap. The test subject's arms will then be measured in the following manner for the demarcation of the 250 cm$^2$test area:

*ii) Measurement of 250$^2$ cm areas*

The determination of the 250 cm$^2$ area of each subjects' forearms is based on the assumption that they approximate a truncated cone shape. The subject's elbow will be placed on a table top with the forearm held perpendicular to that surface. A mark will be made on the upper forearm 3 inches from the table top. A second mark will be made on the lower forearm at a point just below the wrist bone. The circumference of the arm will be measured at each of these points. The average of the two circumferences will be calculated. This represents the approximate circumference at the center point between the two marks. A third mark will be made at the center point between the two marks. The average circumference will be divided into 250cm$^2$, the total exposed surface area required for the test. This will yield the length of arm required to be exposed. The end points of this length of exposure area will be marked on the forearm so that each end point is equidistant from the center point. The endpoint measurements from the center point will be recorded so that they may be duplicated in the test. The distance from the tip of the

little finger to the center point will be measured and also recorded so that the center point may be duplicated at another time.

The above mentioned measurements will be recorded on a repellent measurement form. If a test subject has been previously measured, the existing measurements will be used.

iii) *Delineation of 250$^2$ cm areas*

The test subjects and the control subject will have 250 cm$^2$ areas delineated around their forearms and these arms will be prepared for treatment. The skin above and below the target area will be protected with elastic bandages and or Velcro® straps held in place with Elastikon® tape. Arms will be protected by shirt sleeves. Latex or vinyl gloves will be given to the subjects to protect their hands.

*iv) Determination of Attractancy to Stable Flies*

Test subjects will be checked for their attractiveness to stable flies. Subjects will place their right forearm into their cage and the number of flies landing on their arms will be counted. The required landings will be at least 2 stable flies in 60 seconds to qualify a subject as being attractive to the flies. Volunteer will repeat the qualifying exposure as above using the left arm. The procedure will be repeated if the subject fails to qualify. If a subject again fails to qualify after repeated exposures, that subject may be dropped from the study.

After qualification the test subjects will be treated with the two repellent products.

*v) Treatment*

The repellents will be coded as "A" (cream) or "B" (spray), and each arm will be labeled on the protective wrap with the code corresponding to the repellent applied. Each test subject will be treated on the right arm with repellent "A" and on their left arm with repellent "B".

The test articles will be applied to the test subjects using a syringe (minus needle), rubbed on by hand by an ICR staffer using their surgically-gloved hands. If the cream repellent is too viscous to be applied with a syringe, it will be applied with a cotton-tipped applicator stick. The amount of test article applied will be determined in the dose range finding. The hands will be protected with gloves. The control subject will receive no treatment. In the case of the spray, the product will be dispensed into a 250 ml beaker after which it will be applied by syringe (minus needle). Application of the spray will differ from the manner in which it will be used by consumers or in the dose determination phase of the study. Application by syringe is, however, required to allow accurate measurement for equal treatment.

Subjects will be treated in pairs. Both members of a pair will be treated with the cream and then with the spray. The time of treatment will be the time when the application of the spray treatment

begins. This time will represent the starting time used for calculation of the protection times afforded by the test articles.

**h) Testing**

A group of 25 stable flies will be placed in each test cage prior to the first exposure period. The aggressiveness of the caged stable flies prior to each exposure period will be determined from the landing rate on the control's arm before each test exposure. Once the landing rate has been confirmed (at least 2 landings in 60 seconds), the counts will cease. The landing rate verification will be conducted before each exposure of the treated test subjects. If fewer than the required number of stable flies land in 60 seconds, a new group of 25 stable flies will be released into that cage (as well as into the other 5 cages so as to avoid bias) after the old flies have been removed with a vacuum.

ICR staff will assist the test subjects in inserting their arms into the test cages, taking care not to rub them on the cloth sleeve. The test subjects will expose their treated forearms to the stable flies for 5 minutes. The subjects will then remove their arms from the cages with assistance from an ICR staff. Exposures to the stable flies will be repeated every 30 minutes until the treatment on any given forearm is determined to be no longer effective or until 10 hours have elapsed, whichever occurs first.

The test data to be recorded will be bites. Test data will be recorded on a Repellency Test Data Sheet.

**i) Rationale for using Bites instead of Landings as the End Point**

Bites will be used as the end point instead of landings in this test for the following reasons.

i). A fly which has been allowed to bite after it lands (takes blood into its abdomen) is less likely to land again than a fly which was brushed away after its first landing before it could bite to take blood. This fly will probably land again so it can get the blood meal it needs. This one fly could thus account for both the first landing and the second (confirming) landing. Aspirating stable flies once they land will frequently not be successful since they are elusive flyers and cannot always be captured on the first attempt by aspiration once they have landed (this was tried at ICR during protocol development). In such cases, the fly which landed cannot be identified from among the other 24 flies in the cage for subsequent attempts at aspiration. Once a stable fly has bitten and fed, however, it is much less likely to bite again as it will have accomplished its goal of securing a blood meal. Using bites therefore will greatly increase the chances that two different flies will be involved in the determination that the repellent product has lost its repellency (broken down).

ii). Unlike field testing of mosquitoes, where there is the possibility of a bite transmitting a disease, these lab-reared stable flies do not carry disease.

iii). The bite of a stable fly usually results on in transient pain only, without the ensuing itching and welting associated with mosquito bites.

iv). Stable flies in the wild usually land on one's ankles and lower legs. Therefore, if they only land and do not bite, one may not even notice them. It is only when they bite that they become a nuisance. It is more important therefore to demonstrate that the repellent prevents bites rather than landings.

v). Stable flies often land long before they bites. A conservative analysis of 9 stable fly tests conducted by ICR from 1990 to 1999 revealed that the time difference between first confirmed landing and first confirmed bite ranged from 0 to 7.5 hours with a mean of 2.6 hours. Therefore ladings would seriously underestimate the protection time for the test products.

**i. Criteria for Test End Point**

The test subjects will continue to expose their treated arms to stable flies until the FCB (First Confirmed bite) or until 10 hours have elapsed, whichever occurs first. The FCB occurs when two bites occur on the same arm in the same exposure period, or one bite occurs in each of two consecutive exposure periods (the first bite being the confirmed bite) A bite is defined as a stable fly penetrating the skin with its proboscis and taking blood into its abdomen. When the two bites have occurred as noted above, the test will terminate on that arm.
The test will be terminated on each treated arm after an FCB occurs. The subject will then be able to remove the bandages and tape, scratch and wash that arm. If they want to, they can use rubbing alcohol to help stop any itching from bites they have received. Caladryl® or Calamine® lotion may also be used. When the testing is terminated for the first arm, the subject will roll down their sleeve on that arm.

If a single bite occurs without a confirming second one within that exposure or the following one, that bite will not count towards product breakdown – two additional bites, within one or two consecutive exposures, will be required.

## 22. CONFIDENTIALITY

The information obtained from test subjects taking part in this test may be used by ICR and its sponsor and may become part of a report. This report will be kept as confidential as possible under local, state and federal law. The test subjects' first and last initial and their dedicated identity number only may be referenced. ICR cannot guarantee that the subjects' identity will be kept confidential. Essex Institutional Review Board has the right to review the subjects' records.

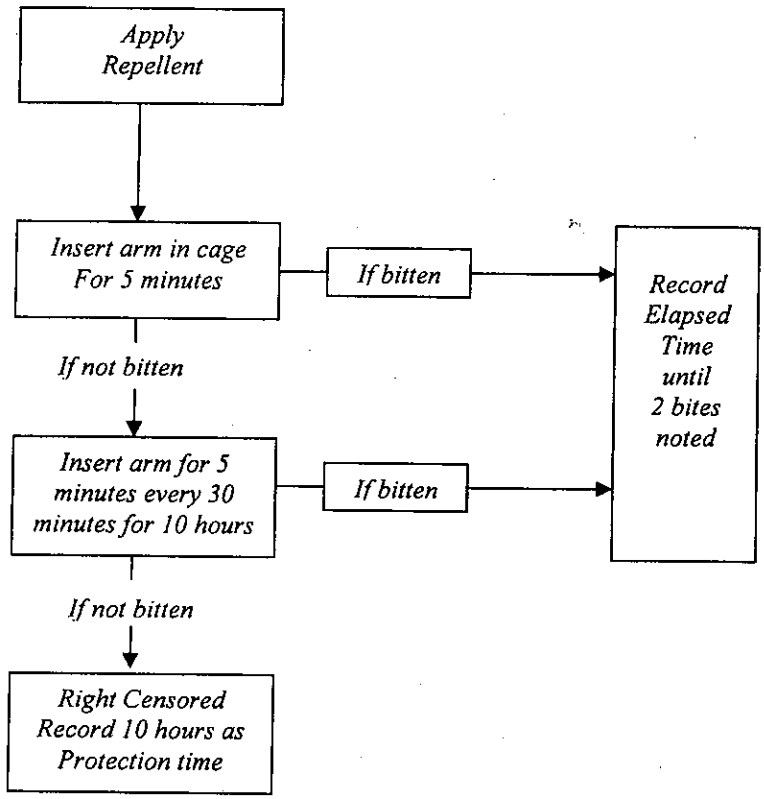
## 23. DATA ANALYSIS

**a) Goals**

The purpose of this study is to determine the extent to which a stable fly repellent is effective in preventing bites on exposed human skin. The repellent will be considered degraded if either of these two conditions is met: a) two stable fly bites are noticed in a single 5 minute observation period; or, b) a single bite in two adjacent observation periods is noted. The goal of the study is to provide an estimated length of protection time from a first confirmed bite (FCB) that a specific repellent provides.

**b) Methodology**

Individuals will have repellent applied to a specific area of their forearms. Then, their arms will be exposed to live stable flies for five minutes. If two bites are noted in this time period, the case will be considered a "bite". If no bites are noted, the arm will be removed and re-exposed 30 minutes later for another 5 minutes. This process will continue either till two bites are noted or 10 hours have elapsed. The methodology is graphically presented below:




Subjects will be assessed for product efficacy every 30 minutes over the 10 hour study interval. Thus for each complete subject, there will be 20 assessments of protection efficacy (2 assessments per hour X 10 hours).

**c) Statistical Procedures:**

***Power.*** Based on a meta-analysis of mosquito studies of this type, Rutledge and Gupta (1999) provided power tables for determining the number of subjects needed to determine protection times up to 8 hours with varying confidence limits and two-tail levels of significance. Using information from their), 11 subjects would be necessary in order to have a 95 % confidence interval for assessing protection up to 8 hours with a ± 2 hour confidence limit.

The proposed study will use stable flies as the test organism, not mosquitoes. Stable fly behavior differs from that of mosquitoes, a meta-analysis for the former species is needed for a confident prediction of the sample size needed for a reliable estimate of protection time. ICR is unaware of

any such study. We analyzed our own data base consisting of 9 stable fly repellent studies conducted between 1900 and 1999 in which the numbers of subjects ranged from 2 to 10. Our consulting statistician is of the opinion that the data are inadequate for deriving a reliable power estimate table, especially as many of the protection times were left (<0.5 hours) or right (>8 hours) censored. When these data had been excluded, the remaining data did not show survival time being significantly linked to standard deviation. With these caveats and following the procedures outlined by Rutledge and Gupta (1999), he derived the table shown below for 95% confidence levels, two-tailed with a 2-hour confidence interval.

| Time (in hours) | Standard Deviation | Sample Size |
|---|---|---|
| 1 | .95 | 1 |
| 2 | 1.18 | 2 |
| 3 | 1.42 | 2 |
| 4 | 1.65 | 3 |
| 5 | 1.89 | 4 |
| 6 | 2.12 | 5 |
| 7 | 2.35 | 6 |
| 8 | 2.59 | 7 |

The table indicates that a sample size of seven subjects would be adequate. In view of the uncertainties noted above relating to this table, we have chosen to run this study with twelve subjects in an effort the minimize the risk of interpreting repellent protection from a too small data set.

**d) Analyses.**

Data will be analyzed using SPSS v. 16 software. The Kaplan-Meier (KM) product-limit technique will be used to describe and analyze the length of time to product degradation. KM allows for the presence of right censored data and provides survival proportions as well as mean survival times with corresponding confidence intervals accordingly. Because the KM procedure is based on proportions, there is no need for the underlying scores to be normally distributed. From the KM analysis we will take the mean and median survival times along with its 95% confidence interval as the final result of this study.

In the event that *all* subjects right censor (i.e., last the entire 10 hours without any bites), we will conclude, with 95% confidence, that the product can provide protection for up to 8 hours, ± 2 hours.

In the event that *more* than two subjects drop out during the study, final estimates of protection time will be made that are consistent with the power parameters stated above.

## 23. QAU AND DATA ARCHIVING

Good Laboratory Practices, as outlined in 40 CFR §160 will be followed throughout the study. The QAU representative will observe and write phase report(s) for this study. All data will be archived.

## 24. SCHEDULE OF EVENTS

| DATE | PROCEDURE |
|---|---|
| Time Zero | Test Conducted |
| At End of Test | Verbal Report |
| After The Laboratory Test Conduct | Written Report |
| After Final Report Has Been Issued | Test articles Returned |

## 25. STATEMENT OF AMENDMENT OR DEVIATION

Any amendments to this protocol must be discussed with and approved by the Sponsor.
Any amendments to, or deviations from, this protocol will be documented in the final report.

Robin G. Todd PhD, BCE
Director, ICR, Inc. 1/23/08 Date

Ellen W. Quinn 1/23/08
QAU, ICR Inc. Date

William J. Gaynor 1/23/08
Study Director, ICR Inc. Date

G.K. Sangha 1-22-08
G.K. Sangha PhD
Representative Date
LANXESS corporation

**APPENDIX I:**
**DATA COLLECTION SHEETS**

**RAW DATA COLLECTION SHEET**

SPONSOR: 433 DATE: TIME:
S D/TECH: William J. Gaynor SPECIES: S. *calcitrans*

PRE-TEST LANDING RATES

SUBJECT Initial and Number:

| TIME (SECONDS) REQUIRED FOR 2 LANDINGS | |
|---|---|
| RIGHT FOREARM | LEFT FOREARM |
| | |
| | |
| | |
| | |
| | |

Signatures of Study Associates Recording data on this sheet/date: .....
Study Director's Signature/Date .....
Test Subject's Initials/Date .....

**RAW DATA COLLECTION SHEET**

SPONSOR: 433 DATE: START TIME:
S D/TECH: William J. Gaynor SPECIES: S. *calcitrans* TEST ARTICLE APPLIED BY:

| TEST ARTCL | SUBJ ECT NUMBER: | | SUBJ ECT NUMBER: | | CONTROL SUBJECT No. :_____ |
|---|---|---|---|---|---|
| | | | | | TIME FOR 2 LANDINGS (seconds) |
| TIME (Hours) | RIGHT ARM BITE | LEFT ARM BITE | RIGHT ARM BITE | LEFT ARM BITE | |
| 0.5 | | | | | |
| 1.0 | | | | | |
| 1.5 | | | | | |
| 2.0 | | | | | |
| 2.5 | | | | | |
| 3.0 | | | | | |
| 3.5 | | | | | |
| 4.0 | | | | | |
| 4.5 | | | | | |
| 5.0 | | | | | |
| 5.5 | | | | | |
| 6.0 | | | | | |
| 6.5 | | | | | |
| 7.0 | | | | | |
| 7.5 | | | | | |
| 8.0 | | | | | |
| 8.5 | | | | | |
| 9.0 | | | | | |
| 9.5 | | | | | |
| 10.0 | | | | | |
| FAIL | | | | | |

Signatures of Study Associates recording data: .....Study Director's Signature/Date .....
Test Subject's Initials/Date _____

# Repellent Measurements–Arm

SUBJECT:

DATE:

**LEFT ARM**

LOWER ARM =

AVG = 250 cm = = 2

UPPER ARM =

CENTER POINT = DISTANCE FROM LARGE TO SMALL CIRCUMFERENCE _____ cm. = 2

DISTANCE FROM CENTER POINT TO TIP OF LITTLE FINGER

DISTANCE FROM EITHER SIDE OF CENTER POINT

**RIGHT ARM**

LOWER ARM =

AVG = 250 cm = = 2

UPPER ARM =

CENTER POINT = DISTANCE FROM LARGE TO SMALL CIRCUMFERENCE _____ cm. = 2

DISTANCE FROM CENTER POINT TO TIP OF LITTLE FINGER

DISTANCE FROM EITHER SIDE OF CENTER POINT

DATA TRANSFER VERIFIED BY:_____DATE:

## APPENDIX II:
## INFORMED CONSENT DOCUMENT – DOSE DETERMINATION

Test subject's initials:.....

Date:.....

**PROTOCOL:** EVALUATION OF THE EFFICACY OF KBR 3023 (PICARIDIN; ICARIDIN) – BASED PERSONAL INSECT REPELLENTS (20% CREAM, 20% SPRAY) AGAINST STABLE FLIES IN THE LABORATORY

## INFORMED CONSENT AUTHORIZATION TO PARTICIPATE IN THE DOSE DETERMINATION PHASE OF AN ICR, INC. STABLE FLY REPELLENT EVALUATION IN THE LABORATORY

**Principal Investigator: William J. Gaynor**
**Address: ICR, Inc. 1330 Dillon Heights Ave. Baltimore, MD**
**Telephone Number: 410-747-4500**
**24 Hour Emergency Number: 410-207-0415**

**Purpose of Study**

We (ICR, Inc.) have been contracted by LANXESS Corporation to conduct a research study in our laboratory on two insect repellent products containing the active ingredient picaridin, to find out how well these products repel stable flies. Before this study can be performed the dose of the two repellents to be used in the study must be determined based on how much product a typical consumer would apply to themselves. This dose determination phase of the study is the study for which we are asking you for your participation. This dose determination phase of the study will occur in the ICR, Inc. lab where the stable fly repellents will later be tested using the doses you determine today. We have prepared this Informed Consent Document (ICD) to explain this dose determination study to you so that you can make a free choice whether or not to participate.

We will review this document with you to make sure you understand what would be expected of you if you participate, and to explain the risks you would face through your participation. Please ask us about anything you do not understand. If you have
have come into our office to review the document, you may take it home with you if you need more time to think about whether to participate.

Test subject's initials:.....

Date:.....

We will apply the eligibility standard listed on the next page to determine if you qualify to participate in the study. If you qualify, we will ask you to consider signing this document to indicate your consent to participate. Your singing indicates your willingness to participate in this study, but you would still be free to withdraw from the study at any time, without having to give a reason.

If you decide you would like to participate, initial each page of this form and sign the last page in the presence of someone on the ICR staff. The Principal Investigator will sign the form as well, and you will be given a copy with both signatures. We will notify you by phone within one week whether you have been selected for the study.

**Eligibility for the Study**

To participate in this study you must meet the following conditions:

- Sex: No exclusions
- Age: You must be at least 18 and not over 70
- Race: No exclusions
- Literacy: You must be able to read, speak, and understand English
- You must not be pregnant or breastfeeding. If you are female, you will be required to perform an over-the-counter urine pregnancy test on the morning of the study. ICR will provide the test kit, and a female ICR staff member will verify the results. ICR will keep the results of the pregnancy test confidential from everyone except you and the Principal Investigator.
- You must not be an employee or a relative of an employee of ICR Inc., LANXESS Corporation, or any other party with an interest in this research.
- You must have no known sensitivity to insect repellents or to skin care products

If you choose to participate in this study and are selected to be a study subject, you must also agree

Test subject's initials:.....

Date:.....

- To follow the directions of the Principal Investigator and other ICR staff.

- Not to use tobacco, alcohol, or any scented cosmetic products after 8 p.m. the night before study, and on the day of the study until it is concluded.

**Dose Determination Phase Summary**

Twelve subjects will participate in this one-day laboratory study. Each of you will apply the cream repellent and the spray repellent to your arms three times. You will apply as much as you normally would, without any instructions from us as to how much to apply. We will measure the amount of repellent you applied and average that amount with the amount the other participants applied to determine the dose to be used in the repellent study. This study will take less than 9 hours for all 12 test subjects. If you finish early, you will be allowed to leave earlier. The entire test will be conducted in a room maintained at comfortable ambient temperature and humidity.

**Procedures**

On the day of the study, before the test begins:

- We will review this document with you and answer any additional questions you may have since you have signed it.

- You will wash your arms with unscented Neutrogena soap.

- We will measure and mark a 3 to 5 inch wide test area around each of your forearms as described in detail below.

- You will apply the spray and cream repellents three times to the treated area of your forearms in the amount that you would normally apply.

- We will weigh the amount of repellents you and the other 11 test subjects applied and average them to determine a testing dose.

Test subject's initials:.....

Date:.....

**Here is how that will work in detail**

**Laboratory Study Details**

1. All 12 of you will be involved in treating your forearms with each of the two repellent products.

2. We will measure the distance around your arm at the wrist and the elbow, and calculate how wide a band is needed for the standard test area on your arm. This 3 - 5 inch wide band will be wider on thinner arms; narrower on bigger arms. We will then use a felt-tip pen to mark the location of the band around each of your forearms.

3. We will cover the skin above and below the marked test area with multiple layers of elastic bandages and or Velcro® straps held in place with adhesive tape.

4. You will then put on a latex or vinyl glove and use a gloved finger to apply the cream repellent to the treatment area of your forearm until you feel you have applied the amount of repellent you would apply if you were applying it at home.

5. We will determine how much product you applied by weighing the repellent container before and after you use it.

6. You will apply the cream repellent a total of three times in the same way. Between applications you will wash your forearm with unscented Neutrogena soap until you feel that you have washed off all the repellent. You will then dry your arm with a paper towel and then let it air dry until your arm feels completely dry.

7. We will then measure the amount of the spray repellent you would typically apply. We will take an average of your three applications and of all the other subjects. Finally we will take an average of these 12 subject averages.

8. We will wrap a 2 inch wide strip of waterproof dressing around the middle of the test area on your arm (waterproof side against your skin). Then we will wrap a 2 inch

wide band of surgical gauze around the dressing. We will secure the gauze and the dressing with two rubber bands. Your forearm will now have a band of dressing (with gauze on top) and bare skin on either side.

9. You will then spray the second repellent over the entire marked out treatment band area of your forearm (including the gauze-covered dressing) until the amount of product you have applied to the two bare skin areas of your forearm feels like what you would apply if you were using the product at home.

10. We will remove the gauze-covered dressing and weigh it to calculate the amount of product you applied.

11. You will repeat this spraying process two more times, washing and drying your forearm as you did with the cream repellent between applications. We will use new bands of dressing and gauze for each of the three sprayings.

12. Once you have applied both the cream and repellents three times, your involvement in the test is done. You may remove your bandages, wash your forearms, and go home.

13. The day's study may last up to nine hours for all 12 test subjects, although your direct involvement should not last more than three hours. You may either bring your own lunch or pay to have lunch ordered.

**Discomfort and Hazard**

Test subject's initials:.....

Date:.....

**You will be exposed to one type of risk throughout the duration of this study.**

**Reaction to the test repellents**

You may have a reaction to the test repellents.

The Sponsor has minimized this possibility by choosing an active ingredient (picaridin) that has demonstrated low acute oral, skin, and inhalation toxicity. The Environmental Protection Agency (EPA) has classified it as low toxicity for acute inhalation toxicity and primary skin irritation. EPA has classified the two test repellents as having low to mild toxicity based on eye irritation. For this reason it is important not to rub your eyes with your treated arms. The Sponsor has selected the non-repellent ingredients in the formulations because they are widely used in cosmetics and have a long history of safe use. ICR staff will be monitoring all subjects for any signs of a reaction to the test repellents. If you think you may be having such a reaction, tell a member of the staff immediately.

The temperature and humidity conditions present in the laboratory will be those maintained in a typical office environment and as such should be comfortable to most people.

Should you have any medical problems, we will have First- Aid- qualified staff members, and First- Aid- supplies on site. We will have cell phones to make emergency calls if necessary. In the case of medical emergency, we will transport you to a selected local hospital at our expense. We will pay all of your medical bills for study-related illnesses and injuries. The Principal Investigator will contact you by telephone, two weeks after the study to ask if you have experienced any adverse effects. You should contact the Principal Investigator any time after the study if you experience any study-related adverse effects, either before or after this follow up call.

**Financial Consideration**

Test subject's initials:.....

Date:.....

We will pay you $11/hour for the 9 hour duration of the study for a total payment of $99 paid to you. This payment will be mailed to you on the 15th or the last day of the month. If we ask you to drop out of the test, and you have complied with all of our requests, you will still receive full payment. If we ask you to drop out of the test because you have not followed all of our directions, or if you choose to drop out of the test, we will compensate you for time up to that point at the rate of $11 per hour.

**Costs**

There are no financial costs to you for participating in this study.

**Benefits**

You will get no personal benefit from participating in this study. The main benefit of this dose determination study is that it establishes the dose of the repellents to be tested in the subsequent stable fly repellent study. The sponsor, LANXESS Corporation will gain the most direct benefit from the conduct of the repellent study, which is expected to support additional marketing claims that these products repel stable flies.

Some benefit is also likely to result for society in general through showing the effectiveness of these products in repelling a potentially important public health pest.

**Your Rights**

We will give you an opportunity to discuss with us any aspects of this document or of the study it describes that are not clear to you, so that you fully understand the nature of the study, its purpose, and the procedures to be used, as well as the discomforts, and risks you may experience during or after the study. You are encouraged to ask questions at any time, before or after you consent to participate, and before, during, or after the study day itself. Your participation is entirely voluntary. You may decide not to take part in this study, and if you decide you would like to participate, you are free to change your mind at any time without having to explain, and without penalty or loss of benefits to which you may be otherwise entitled.

Test subject's initials:.....

Date:.....

**Alternative**

The only alternative to participating is for you to decide not to.

**Questions**

If you have any questions about this study or suffer a reaction you think might be associated with the study, call us at 410-747-4500. If you have any questions about your rights as a research participant, or related concerns, you may contact the Essex Institutional Review Board (IRB), 121 Main Street, Lebanon, NJ 08833, telephone 908-236-7735. The Essex IRB is a committee that has reviewed this research project to help ensure that the rights and welfare of the participants are protected and that the study is designed and carried out ethically. Review of this study by the Essex IRB is not an endorsement of the study or its outcome.

**Confidentiality**

We and the sponsor or its agents may use the information obtained from your taking part in this test, and this information may become part of a report. We will keep your participation as confidential as possible referring to you in the study data and reports only by your initials or an arbitrary ICR identification. However, we cannot guarantee that your identity will be kept confidential; the sponsor, personnel associated with the study, a regulatory agency such as the Environmental Protection Agency (EPA), and the Essex Institutional Review Board (EIRB) all have a right to review your records.

Test subject's initials:.....

Date:.....

**Consent**

I voluntarily agree to participate in this study. I will be given a copy of this signed form. By signing this form I have not given up any of my legal rights.

| | | | |
|---|---|---|---|
| Signature of Subject | Date | Signature of Witness | Date |

| | |
|---|---|
| Signature of Principal Investigator | Date |

Test subject's initials:.....

Date:.....

## APPENDIX III:
## INFORMED CONSENT DOCUMENT – REPELLENT TEST

Test subject's initials:.....

Date:.....

**PROTOCOL:** EVALUATION OF THE EFFICACY OF KBR 3023 (PICARIDIN; ICARIDIN) – BASED PERSONAL INSECT REPELLENTS (20% CREAM, 20% SPRAY) AGAINST STABLE FLIES IN THE LABORATORY

## INFORMED CONSENT AUTHORIZATION TO PARTICIPATE IN AN ICR, INC. STABLE FLY REPELLENT EVALUATION IN THE LABORATORY

**Principal Investigator: William J. Gaynor**
**Address: ICR, Inc. 1330 Dillon Heights Ave. Baltimore, MD**
**Telephone Number: 410-747-4500**
**24 Hour Emergency Number: 410-207-0415**

**Purpose of Study**

We (ICR, Inc.) have been contracted by LANXESS Corporation to conduct a research study in our laboratory on two insect repellent products containing the active ingredient picaridin, to find out how well these products repel stable flies. The stable flies used in this study are laboratory-reared and do not carry any diseases. This study will take place in the ICR, Inc. lab with stable flies confined in cages. This document will explain the study to you so that you can make a free choice whether or not to participate.

We will review this document with you to make sure you understand what would be expected of you if you participate, and to explain the risks you would face through your participation. Please ask us about anything you do not understand. If you have
have come into our office to review the document, you may take it home with you if you need more time to think about whether to participate.

We will apply the eligibility standard listed on the next page to determine if you qualify to participate in the study. If you qualify, we will ask you to consider signing this document to indicate your consent to participate. Your signing indicates your willingness to participate in this study, but you would still be free to withdraw from the study at any time, without having to give a reason.

Test subject's initials:.....

Date:.....

If you decide you would like to participate, initial each page of this form and sign the last page in the presence of someone on the ICR staff. The Principal Investigator will sign the form as well, and you will be given a copy with both signatures. We will notify you by phone within one week whether you have been selected for the study.

**Eligibility for the Study**

To participate in this study you must meet the following conditions:

- Sex: No exclusions
- Age: You must be at least 18 and not over 70
- Race: No exclusions
- Literacy: You must be able to read, speak, and understand English
- You must be attractive to stable flies, as evidenced by at least 2 landings of caged stable flies on your untreated forearm within one minute.
- You must not be pregnant or breastfeeding. If you are female, you will be required to perform an over-the-counter urine pregnancy test on the morning of the study. ICR will provide the test kit, and a female ICR staff member will verify the results. ICR will keep the results of the pregnancy test confidential from everyone except you and the Principal Investigator.
- You must not be an employee or a relative of an employee of ICR Inc., LANXESS Corporation, or any other party with an interest in this research.
- You must have no known sensitivity to stable fly bites, to insect repellents, or to skin care products

If you choose to participate in this study and are selected to be a study subject, you must also agree :

- To follow the directions of the Principal Investigator and other ICR staff.
- Not to use tobacco, alcohol, or any scented cosmetic products after 8 p.m. the night .

Test subject's initials:.....

Date:.....

before study, and on the day of the study until it is concluded.

- To wear proper protective clothing on the day of the study: blue jeans or other sturdy trousers, heavy socks, long sleeve shirts, and gloves. Gloves will be provided by ICR. The heavy clothing will help protect you from any stable flies which escape from the cages during testing.

**Laboratory Repellent Phase Summary**

Thirteen subjects will participate in this one-day laboratory study over a period of about 11 hours. One of you will be selected by lot to serve as the "control subject", and will not be treated with the test repellents. The other 12 subjects will be "treated subjects", and will be treated with both of the repellents, one on each forearm. The entire test will be conducted in a room maintained at comfortable ambient temperature and humidity.

Every 30 minutes during the test, the untreated control subject will put one untreated forearm into each test cage containing 25 stable flies for one minute. If fewer than 2 stable flies land within one minute, the stable flies will be vacuumed from all 6 test cages and 25 more stable flies will be added to each cage to ensure enough activity for a valid test.

After the untreated control subject has verified adequate stable fly activity, the 12 treated subjects will carefully put both forearms into their assigned cage with the stable flies for five minutes.

This pattern will be continued every half hour until you receive either two stable fly bites on the same arm in the same 5-minute exposure period, or one bite in each of two consecutive 5-minute exposure periods, or until ten hours after your treatment, whichever happens first.

**Procedures**

On the day of the study, before the test begins:

- We will review this document with you and answer any additional questions you may have since you have signed it.
- You will wash your arms with unscented Neutrogena soap.
- We will measure and mark a 3 to 5 inch wide test area around each of your forearms as

described in detail below.

- After we have measured your arms and protected the skin outside the test area, we will determine your attractiveness to stable flies as described below.

- Unless you are selected as the untreated control subject, we will treat both your arms with test repellents and the study will begin.

**Here is how that will work in detail**

**Laboratory Study Details**

1. One of you will be selected by lot to be the untreated control subject.

2. We will measure the distance around your arm at the wrist and the elbow, and calculate how wide a band is needed for the standard test area on your arm. This 3 - 5 inch wide band will be wider on thinner arms; narrower on bigger arms. We will then use a felt-tip pen to mark the location of the band around each of your forearms. The control subject will be measured and marked on only one forearm.

3. We will protect the skin above and below the marked test area from stable fly bites with multiple layers of elastic bandages and or Velcro® straps held in place with adhesive tape.

4. We will verify that you are attractive to stable flies. You will put one forearm into a test cage containing 25 stable flies, and we will count the number of stable flies landing on your arm. We will brush landing stable flies off your arm before they have a chance to bite you. If 2 stable flies land on your arm in a minute or less you will qualify as "attractive". You will then repeat the same procedure with your other arm. If you are not attractive after one attempt, you may repeat the process a second time. If you fail to attract stable flies in two trials you may not be eligible to participate in the study.

5. If you are a treated subject, we will apply one of the repellents to the test area on each of your forearms, using a syringe without the needle. The amount of repellent applied

Test subject's initials:.....

Date:.....

will be a standardized "typical consumer dose". This amount will always be less than a quarter of a teaspoonful. If you are the untreated control subject, you will receive no treatment.

6. With a fingertip in a latex or vinyl glove, we will spread the repellent evenly over the test areas. Once your arms have been treated, you must be careful not to rub them against anything, as this could rub off some of the test repellent and change the results of the study.

7. We will mark your bandages with a letter identifying the repellent applied to that arm. We will not identify the repellents to you.

8. You will go to the test laboratory and wait for your repellents to dry for about one-half hour. Then you will put on gloves to protect your hands from bites, ready for your first 5-minute exposure period of the day.

9. ICR staff will show you which cage to use. Treated subjects will work in pairs. If you see a stable fly land on your own or your partner's arm, notify ICR staff.

10. Every 30 minutes after the test begins, the untreated control subject will put one arm into each of the six test cages in turn, to verify stable fly activity. As soon as 2 stable flies land, the control subject will remove his or her arm from the cage. If fewer than 2 stable flies land on the control subject's arm within one minute, all of the flies in each of the 6 test cages will be vacuumed out and replaced with 25 fresh stable flies. ICR staff will brush away any landing stable flies from the control subject before the flies have time to bite. Nonetheless it is likely that the control subject will get some bites during the course of the study.

11. Every 30 minutes after the study begins, after the activity of the stable flies in their assigned cage has been verified, each pair of treated subjects will carefully put both their arms into the cage for 5 minutes. During the 5-minute exposure period we will count the number of stable flies (up to two) that bite the treated skin of either of your arms. When you receive two bites on the same arm in one exposure period, or

one bite in each of two consecutive exposure periods, you will remove that arm from the cage and from the study. We will call this "breakdown", and once you reach breakdown on one of your arms you will no longer expose that arm for the rest of the day's study. You can then remove the bandages and tape from this arm, and scratch if you choose. Caladryl®, Calamine® lotion and rubbing alcohol will be provided to help stop any itching from bites you received. When you reach breakdown on both arms, you will have finished your part in the study and may go home.

12. After each 5-minute exposure period you may leave the test room, but you must remain in the lab. You can go to the restroom if you need to, and the Study Director will call breaks every few hours. You may either bring your own lunch or pay to have lunch ordered.

13. After preparation and treatment of subjects, which will take about one hour, the day's study will include up to 20 5-minute exposure periods at 30 minute intervals over 10 hours. The study will end after 10 hours or when all treated test subjects have reached breakdown on both arms, whichever comes first.

**Discomfort and Hazard**

**You will be exposed to two types of risk throughout the duration of this study.**

**Stable fly bites**

A bite occurs when a stable fly lands and sticks its pointed mouthparts into your skin and takes blood. A stable fly bite will cause momentary pain and leave a small red mark which will usually disappear within a couple of days. The pain from a stable fly bites usually stops as soon as it stops biting. The irritation and swelling, which often result from mosquito bites, are not nearly so common after stable fly bites. In severe cases, a bite or probe may cause the development of large bumps on your skin, difficulty breathing, sweating and/or a rapid pulse. For some people this could be life-threatening.

Test subject's initials:.....

Date:.....

All subjects will be exposed to stable flies for at least 1 minute to verify attractiveness to stable flies. Although we will try to brush the stable flies off before they bite, there is a slight possibility of being bitten. Treated subjects will expose their forearms to stable flies for five minutes every half hour. Although they will not expose an arm further if they receive two bites on it in one exposure, or one bite in two consecutive exposure periods, they may receive more than two bites on each arm during the test. A bite which is not followed by another bite in the same or the next exposure will be disregarded. If you are a treated subject you will still need to receive at least two more bites on that arm to reach breakdown. The untreated control subject will be exposed to stable flies every half hour for up to one minute in each of six test cages. Although we will try to brush the landing stable flies off before they bite, the control subject is likely to be bitten by some of them. We will minimize the irritation from bites or probes you receive by making Caladryl® or Calamine® lotion or rubbing alcohol available at the study site for your use after the study is completed.

**Reaction to the test repellents**

You may have a reaction to the test repellents.

The Sponsor has minimized this possibility by choosing an active ingredient (picaridin) that has demonstrated low acute oral, skin, and inhalation toxicity. The Environmental Protection Agency (EPA) has classified it as low toxicity for acute inhalation toxicity and primary skin irritation. EPA has classified the two test repellents as having low to mild toxicity based on eye irritation. For this reason it is important not to rub your eyes with your treated arms. The Sponsor has selected the non-repellent ingredients in the formulations because they are widely used in cosmetics and have a long history of safe use. ICR staff will be monitoring all subjects for any signs of a reaction to the test repellents. If you think you may be having such a reaction, tell a member of the staff immediately.

The stable flies being used in this study will be laboratory-reared and disease-free, and they will never have had a human blood meal. There is therefore no risk of your contracting any stable fly-borne disease as a result of participation in this study.

Test subject's initials:.....

Date:.....

The temperature and humidity conditions present in the laboratory will be those maintained in a typical office environment and as such should be comfortable to most people.

Should you have any medical problems, we will have First- Aid- qualified staff members, and First- Aid- supplies on site. We will have cell phones to make emergency calls if necessary. In the case of medical emergency, we will transport you to a selected local hospital at our expense. We will pay all of your medical bills for study-related illnesses and injuries. The Principal Investigator will contact you by telephone, two weeks after the study to ask if you have experienced any adverse effects. You should contact the Principal Investigator any time after the study if you experience any study-related adverse effects, either before or after this follow up call.

**Financial Consideration**

We will pay you $11/hour for the first 9 hours and $17.50 for each additional hour that you spend on the day of the study. The study will last about 10 hours with an additional hour of prep time (11 hours total), with a total payment of $134 paid to you. This payment will be mailed to you on the 15th or the last day of the month. If we ask you to drop out of the test, and you have complied with all of our requests, you will still receive full payment. If we ask you to drop out of the test because you have not followed all of our directions, or if you choose to drop out of the test, we will compensate you for time up to that point at the rate of $11 per hour.

**Costs**

There are no financial costs to you for participating in this study.

**Benefits**

You will get no personal benefit from participating in this study. The sponsor, LANXESS Corporation will gain the most direct benefit from the conduct of this study, which is expected to support additional marketing claims that these products repel stable flies.

Some benefit is also likely to result for society in general through showing the effectiveness of these products in repelling a potentially important public health pest.

Test subject's initials:.....

Date:.....

**Your Rights**

We will give you an opportunity to discuss with us any aspects of this document or of the study it describes that are not clear to you, so that you fully understand the nature of the study, its purpose, and the procedures to be used, as well as the discomforts, and risks you may experience during or after the study. You are encouraged to ask questions at any time, before or after you consent to participate, and before, during, or after the study day itself. Your participation is entirely voluntary. You may decide not to take part in this study, and if you decide you would like to participate, you are free to change your mind at any time without having to explain, and without penalty or loss of benefits to which you may be otherwise entitled.

**Alternative**

The only alternative to participating is for you to decide not to.

**Questions**

If you have any questions about this study or suffer a reaction you think might be associated with the study, call us at 410-747-4500. If you have any questions about your rights as a research participant, or related concerns, you may contact the Essex Institutional Review Board (IRB), 121 Main Street, Lebanon, NJ 08833, telephone 908-236-7735. The Essex IRB is a committee that has reviewed this research project to help ensure that the rights and welfare of the participants are protected and that the study is designed and carried out ethically. Review of this study by the Essex IRB is not an endorsement of the study or its outcome.

**Confidentiality**

We and the sponsor or its agents may use the information obtained from your taking part in this test, and this information may become part of a report. We will keep your participation as confidential as possible referring to you in the study data and reports only by your initials or an arbitrary ICR identification. However, we cannot guarantee that your identity will be kept

Test subject's initials:.....

Date:.....

confidential; the sponsor, personnel associated with the study, a regulatory agency such as the Environmental Protection Agency (EPA), and the Essex Institutional Review Board (EIRB) all have a right to review your records.

**Consent**

I voluntarily agree to participate in this study. I will be given a copy of this signed form.
By signing this form I have not given up any of my legal rights.

Signature of Subject Date Signature of Witness Date

Signature of Principal Investigator Date

Test subject's initials:.....

Date:.....

## APPENDIX IV:
## LABELS FOR PRODUCTS

Test subject's initials:.....

Date:.....

# KBR 3023 Insect Repellent Cream

**Contains Bayrepel™. Long-lasting, effective protection from mosquitoes ticks, biting flies, gnats, chiggers, sand 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:

ACCEPTED
with COMMENTS
In EPA Letter Dated
APR 10 2007
Under the Federal Insecticide, Fungicide, and Rodenticide Act, as amended, for the pesticide registered under EPA Reg. No. 39967-50

# KBR 3023 All-Family Insect Repellent Spray

**Long-lasting, effective protection from mosquitoes, ticks, biting flies, gnats, chiggers, sand flies, 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.:**

ACCEPTED
APR 16 2007
Under the Federal Insecticide, Fungicide, and Rodenticide Act, as amended, for the pesticide Registered under EPA Reg. No. 39967-53

LANXESS

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

LABEL TEXT DATE:

## APPENDIX V:
## PRODUCT TOXICOLOGY

Test subject's initials:.....

Date:.....

## 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 I4-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 $_{a2u}$ globulin accumulation. The toxicology profile by oral route of exposure did not reveal any new targets compared to the dermal route and. 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/200rng/kg/day- the highest dose tested).

Test subject's initials:.....

Date:.....

## 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

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**PROTOCOL:** EVALUATION OF THE EFFICACY OF KBR 3023 (PICARIDIN; ICARIDIN) – BASED PERSONAL INSECT REPELLENTS (20% CREAM, 20% SPRAY) AGAINST STABLE FLIES IN THE LABORATORY

## INFORMED CONSENT AUTHORIZATION TO PARTICIPATE IN THE DOSE DETERMINATION PHASE OF AN ICR, INC. STABLE FLY REPELLENT EVALUATION IN THE LABORATORY

**Principal Investigator: William J. Gaynor**
**Address: ICR, Inc. 1330 Dillon Heights Ave. Baltimore, MD**
**Telephone Number: 410-747-4500**
**24 Hour Emergency Number: 410-207-0415**

**Purpose of Study**

We (ICR, Inc.) have been contracted by LANXESS Corporation to conduct a research study in our laboratory on two insect repellent products containing the active ingredient picaridin, to find out how well these products repel stable flies. Before this study can be performed the dose of the two repellents to be used in the study must be determined based on how much product a typical consumer would apply to themselves. This dose determination phase of the study is the study for which we are asking you for your participation. This dose determination phase of the study will occur in the ICR, Inc. lab where the stable fly repellents will later be tested using the doses you determine today. We have prepared this Informed Consent Document (ICD) to explain this dose determination study to you so that you can make a free choice whether or not to participate.

We will review this document with you to make sure you understand what would be expected of you if you participate, and to explain the risks you would face through your participation. Please ask us about anything you do not understand. If you have have come into our office to review the document, you may take it home with you if you need more time to think about whether to participate.

Test subject's initials:.....

Date:.....

We will apply the eligibility standard listed on the next page to determine if you qualify to participate in the study. If you qualify, we will ask you to consider signing this document to indicate your consent to participate. Your singing indicates your willingness to participate in this study, but you would still be free to withdraw from the study at any time, without having to give a reason.

If you decide you would like to participate, initial each page of this form and sign the last page in the presence of someone on the ICR staff. The Principal Investigator will sign the form as well, and you will be given a copy with both signatures. We will notify you by phone within one week whether you have been selected for the study.

**Eligibility for the Study**

To participate in this study you must meet the following conditions:

- Sex: No exclusions
- Age: You must be at least 18 and not over 70
- Race: No exclusions
- Literacy: You must be able to read, speak, and understand English
    - You must not be pregnant or breastfeeding. If you are female, you will be required to perform an over-the-counter urine pregnancy test on the morning of the study. ICR will provide the test kit, and a female ICR staff member will verify the results. ICR will keep the results of the pregnancy test confidential from everyone except you and the Principal Investigator.
- You must not be an employee or a relative of an employee of ICR Inc., LANXESS Corporation, or any other party with an interest in this research.
- You must have no known sensitivity to insect repellents or to skin care products

If you choose to participate in this study and are selected to be a study subject, you must also agree :

Test subject's initials:.....

Date:.....

- To follow the directions of the Principal Investigator and other ICR staff.

- Not to use tobacco, alcohol, or any scented cosmetic products after 8 p.m. the night before study, and on the day of the study until it is concluded.

**Dose Determination Phase Summary**

Twelve subjects will participate in this one-day laboratory study. Each of you will apply the cream repellent and the spray repellent to your arms three times. You will apply as much as you normally would, without any instructions from us as to how much to apply. We will measure the amount of repellent you applied and average that amount with the amount the other participants applied to determine the dose to be used in the repellent study. This study will take less than 9 hours for all 12 test subjects. If you finish early, you will be allowed to leave earlier. The entire test will be conducted in a room maintained at comfortable ambient temperature and humidity.

**Procedures**

On the day of the study, before the test begins:

- We will review this document with you and answer any additional questions you may have since you have signed it.

- You will wash your arms with unscented Neutrogena soap.

- We will measure and mark a 3 to 5 inch wide test area around each of your forearms as described in detail below.

- You will apply the spray and cream repellents three times to the treated area of your forearms in the amount that you would normally apply.

- We will weigh the amount of repellents you and the other 11 test subjects applied and average them to determine a testing dose.

Test subject's initials:.....

Date:.....

**Here is how that will work in detail**

**Laboratory Study Details**

1. All 12 of you will be involved in treating your forearms with each of the two repellent products.

2. We will measure the distance around your arm at the wrist and the elbow, and calculate how wide a band is needed for the standard test area on your arm. This 3 - 5 inch wide band will be wider on thinner arms; narrower on bigger arms. We will then use a felt-tip pen to mark the location of the band around each of your forearms.

3. We will cover the skin above and below the marked test area with multiple layers of elastic bandages and or Velcro® straps held in place with adhesive tape.

4. You will then put on a latex or vinyl glove and use a gloved finger to apply the cream repellent to the treatment area of your forearm until you feel you have applied the amount of repellent you would apply if you were applying it at home.

5. We will determine how much product you applied by weighing the repellent container before and after you use it.

6. You will apply the cream repellent a total of three times in the same way. Between applications you will wash your forearm with unscented Neutrogena soap until you feel that you have washed off all the repellent. You will then dry your arm with a paper towel and then let it air dry until your arm feels completely dry.

7. We will then measure the amount of the spray repellent you would typically apply. We will take an average of your three applications and of all the other subjects. Finally we will take an average of these 12 subject averages.

Test subject's initials:.....

Date:.....

8. We will wrap a 2 inch wide strip of waterproof dressing around the middle of the test area on your arm (waterproof side against your skin). Then we will wrap a 2 inch wide band of surgical gauze around the dressing. We will secure the gauze and the dressing with two rubber bands. Your forearm will now have a band of dressing (with gauze on top) and bare skin on either side.

9. You will then spray the second repellent over the entire marked out treatment band area of your forearm (including the gauze-covered dressing) until the amount of product you have applied to the two bare skin areas of your forearm feels like what you would apply if you were using the product at home.

10. We will remove the gauze-covered dressing and weigh it to calculate the amount of product you applied.

11. You will repeat this spraying process two more times, washing and drying your forearm as you did with the cream repellent between applications. We will use new bands of dressing and gauze for each of the three sprayings.

12. Once you have applied both the cream and repellents three times, your involvement in the test is done. You may remove your bandages, wash your forearms, and go home.

13. The day's study may last up to nine hours for all 12 test subjects, although your direct involvement should not last more than three hours. You may either bring your own lunch or pay to have lunch ordered.

**Discomfort and Hazard**

Test subject's initials:.....

Date:.....

**You will be exposed to one type of risk throughout the duration of this study.**

**Reaction to the test repellents**

You may have a reaction to the test repellents.

The Sponsor has minimized this possibility by choosing an active ingredient (picaridin) that has demonstrated low acute oral, skin, and inhalation toxicity. The Environmental Protection Agency (EPA) has classified it as low toxicity for acute inhalation toxicity and primary skin irritation. EPA has classified the two test repellents as having low to mild toxicity based on eye irritation. For this reason it is important not to rub your eyes with your treated arms. The Sponsor has selected the non-repellent ingredients in the formulations because they are widely used in cosmetics and have a long history of safe use. ICR staff will be monitoring all subjects for any signs of a reaction to the test repellents. If you think you may be having such a reaction, tell a member of the staff immediately.

The temperature and humidity conditions present in the laboratory will be those maintained in a typical office environment and as such should be comfortable to most people.

Should you have any medical problems, we will have First- Aid- qualified staff members, and First- Aid- supplies on site. We will have cell phones to make emergency calls if necessary. In the case of medical emergency, we will transport you to a selected local hospital at our expense. We will pay all of your medical bills for study-related illnesses and injuries. The Principal Investigator will contact you by telephone, two weeks after the study to ask if you have experienced any adverse effects. You should contact the Principal Investigator any time after the study if you experience any study-related adverse effects, either before or after this follow up call.

**Financial Consideration**

Test subject's initials:.....

Date:.....

We will pay you $11/hour for the 9 hour duration of the study for a total payment of $99 paid to you. This payment will be mailed to you on the 15th or the last day of the month. If we ask you to drop out of the test, and you have complied with all of our requests, you will still receive full payment. If we ask you to drop out of the test because you have not followed all of our directions, or if you choose to drop out of the test, we will compensate you for time up to that point at the rate of $11 per hour.

**Costs**

There are no financial costs to you for participating in this study.

**Benefits**

You will get no personal benefit from participating in this study. The main benefit of this dose determination study is that it establishes the dose of the repellents to be tested in the subsequent stable fly repellent study. The sponsor, LANXESS Corporation will gain the most direct benefit from the conduct of the repellent study, which is expected to support additional marketing claims that these products repel stable flies.

Some benefit is also likely to result for society in general through showing the effectiveness of these products in repelling a potentially important public health pest.

**Your Rights**

We will give you an opportunity to discuss with us any aspects of this document or of the study it describes that are not clear to you, so that you fully understand the nature of the study, its purpose, and the procedures to be used, as well as the discomforts, and risks you may experience during or after the study. You are encouraged to ask questions at any time, before or after you consent to participate, and before, during, or after the study day itself. Your participation is entirely voluntary. You may decide not to take part in this study, and if you decide you would like to participate, you are free to change your mind at any time without having to explain, and without penalty or loss of benefits to which you may be otherwise entitled.

Test subject's initials:.....

Date:.....

**Alternative**

The only alternative to participating is for you to decide not to.

**Questions**

If you have any questions about this study or suffer a reaction you think might be associated with the study, call us at 410-747-4500. If you have any questions about your rights as a research participant, or related concerns, you may contact the Essex Institutional Review Board (IRB), 121 Main Street, Lebanon, NJ 08833, telephone 908-236-7735. The Essex IRB is a committee that has reviewed this research project to help ensure that the rights and welfare of the participants are protected and that the study is designed and carried out ethically. Review of this study by the Essex IRB is not an endorsement of the study or its outcome.

**Confidentiality**

We and the sponsor or its agents may use the information obtained from your taking part in this test, and this information may become part of a report. We will keep your participation as confidential as possible referring to you in the study data and reports only by your initials or an arbitrary ICR identification. However, we cannot guarantee that your identity will be kept confidential; the sponsor, personnel associated with the study, a regulatory agency such as the Environmental Protection Agency (EPA), and the Essex Institutional Review Board (EIRB) all have a right to review your records.

**Consent**

Test subject's initials:.....

Date:.....

I voluntarily agree to participate in this study. I will be given a copy of this signed form. By signing this form I have not given up any of my legal rights.

| Signature of Subject | Date | Signature of Witness | Date |
|---|---|---|---|

| Signature of Principal Investigator | Date |
|---|---|

Test subject's initials:.....

Date:.....

**PROTOCOL:** EVALUATION OF THE EFFICACY OF KBR 3023 (PICARIDIN; ICARIDIN) – BASED PERSONAL INSECT REPELLENTS (20% CREAM, 20% SPRAY) AGAINST STABLE FLIES IN THE LABORATORY

## INFORMED CONSENT AUTHORIZATION TO PARTICIPATE IN AN ICR, INC. STABLE FLY REPELLENT EVALUATION IN THE LABORATORY

**Principal Investigator: William J. Gaynor**
**Address: ICR, Inc. 1330 Dillon Heights Ave. Baltimore, MD**
**Telephone Number: 410-747-4500**
**24 Hour Emergency Number: 410-207-0415**

### Purpose of Study

We (ICR, Inc.) have been contracted by LANXESS Corporation to conduct a research study in our laboratory on two insect repellent products containing the active ingredient picaridin, to find out how well these products repel stable flies. The stable flies used in this study are laboratory-reared and do not carry any diseases. This study will take place in the ICR, Inc. lab with stable flies confined in cages. This document will explain the study to you so that you can make a free choice whether or not to participate.

We will review this document with you to make sure you understand what would be expected of you if you participate, and to explain the risks you would face through your participation. Please ask us about anything you do not understand. If you have have come into our office to review the document, you may take it home with you if you need more time to think about whether to participate.

We will apply the eligibility standard listed on the next page to determine if you qualify to participate in the study. If you qualify, we will ask you to consider signing this document to indicate your consent to participate. Your signing indicates your willingness to participate in this study, but you would still be free to withdraw from the study at any time, without having to give a reason.

Test subject's initials:.....

Date:.....

If you decide you would like to participate, initial each page of this form and sign the last page in the presence of someone on the ICR staff. The Principal Investigator will sign the form as well, and you will be given a copy with both signatures. We will notify you by phone within one week whether you have been selected for the study.

**Eligibility for the Study**

To participate in this study you must meet the following conditions:

- Sex: No exclusions
- Age: You must be at least 18 and not over 70
- Race: No exclusions
- Literacy: You must be able to read, speak, and understand English
- You must be attractive to stable flies, as evidenced by at least 2 landings of caged stable flies on your untreated forearm within one minute.
- You must not be pregnant or breastfeeding. If you are female, you will be required to perform an over-the-counter urine pregnancy test on the morning of the study. ICR will provide the test kit, and a female ICR staff member will verify the results. ICR will keep the results of the pregnancy test confidential from everyone except you and the Principal Investigator.
- You must not be an employee or a relative of an employee of ICR Inc., LANXESS Corporation, or any other party with an interest in this research.
- You must have no known sensitivity to stable fly bites, to insect repellents, or to skin care products

If you choose to participate in this study and are selected to be a study subject, you must also agree :

- To follow the directions of the Principal Investigator and other ICR staff.
- Not to use tobacco, alcohol, or any scented cosmetic products after 8 p.m. the night

Test subject's initials:.....

Date:.....

before study, and on the day of the study until it is concluded.

- To wear proper protective clothing on the day of the study: blue jeans or other sturdy trousers, heavy socks, long sleeve shirts, and gloves. Gloves will be provided by ICR. The heavy clothing will help protect you from any stable flies which escape from the cages during testing.

**Laboratory Repellent Phase Summary**

Thirteen subjects will participate in this one-day laboratory study over a period of about 11 hours. One of you will be selected by lot to serve as the "control subject", and will not be treated with the test repellents. The other 12 subjects will be "treated subjects", and will be treated with both of the repellents, one on each forearm. The entire test will be conducted in a room maintained at comfortable ambient temperature and humidity.

Every 30 minutes during the test, the untreated control subject will put one untreated forearm into each test cage containing 25 stable flies for one minute. If fewer than 2 stable flies land within one minute, the stable flies will be vacuumed from all 6 test cages and 25 more stable flies will be added to each cage to ensure enough activity for a valid test.

After the untreated control subject has verified adequate stable fly activity, the 12 treated subjects will carefully put both forearms into their assigned cage with the stable flies for five minutes.

This pattern will be continued every half hour until you receive either two stable fly bites on the same arm in the same 5-minute exposure period, or one bite in each of two consecutive 5-minute exposure periods, or until ten hours after your treatment, whichever happens first.

**Procedures**

On the day of the study, before the test begins:

- We will review this document with you and answer any additional questions you may have since you have signed it.

Test subject's initials:.....

Date:.....

- You will wash your arms with unscented Neutrogena soap.
- We will measure and mark a 3 to 5 inch wide test area around each of your forearms as described in detail below.
- After we have measured your arms and protected the skin outside the test area, we will determine your attractiveness to stable flies as described below.
- Unless you are selected as the untreated control subject, we will treat both your arms with test repellents and the study will begin.

**Here is how that will work in detail**

**Laboratory Study Details**

1. One of you will be selected by lot to be the untreated control subject.

2. We will measure the distance around your arm at the wrist and the elbow, and calculate how wide a band is needed for the standard test area on your arm. This 3 - 5 inch wide band will be wider on thinner arms; narrower on bigger arms. We will then use a felt-tip pen to mark the location of the band around each of your forearms. The control subject will be measured and marked on only one forearm.
3. We will protect the skin above and below the marked test area from stable fly bites with multiple layers of elastic bandages and or Velcro® straps held in place with adhesive tape.

4. We will verify that you are attractive to stable flies. You will put one forearm into a test cage containing 25 stable flies, and we will count the number of stable flies landing on your arm. We will brush landing stable flies off your arm before they have a chance to bite you. If 2 stable flies land on your arm in a minute or less you will qualify as "attractive". You will then repeat the same procedure with your other arm. If you are not attractive after one attempt, you may repeat the process a second time. If you fail to

attract stable flies in two trials you may not be eligible to participate in the study.

5. If you are a treated subject, we will apply one of the repellents to the test area on each of your forearms, using a syringe without the needle. The amount of repellent applied will be a standardized "typical consumer dose". This amount will always be less than a quarter of a teaspoonful. If you are the untreated control subject, you will receive no treatment.

6. With a fingertip in a latex or vinyl glove, we will spread the repellent evenly over the test areas. Once your arms have been treated, you must be careful not to rub them against anything, as this could rub off some of the test repellent and change the results of the study.

7. We will mark your bandages with a letter identifying the repellent applied to that arm. We will not identify the repellents to you.

8. You will go to the test laboratory and wait for your repellents to dry for about one-half hour. Then you will put on gloves to protect your hands from bites, ready for your first 5-minute exposure period of the day.

9. ICR staff will show you which cage to use. Treated subjects will work in pairs. If you see a stable fly land on your own or your partner's arm, notify ICR staff.

10. Every 30 minutes after the test begins, the untreated control subject will put one arm into each of the six test cages in turn, to verify stable fly activity. As soon as 2 stable flies land, the control subject will remove his or her arm from the cage. If fewer than 2 stable flies land on the control subject's arm within one minute, all of the flies in each of the 6 test cages will be vacuumed out and replaced with 25 fresh stable flies. ICR staff will brush away any landing stable flies from the control subject before the flies have time to bite. Nonetheless it is likely that the control subject will get some bites during the course of the study.

Test subject's initials:.....

Date:.....

11. Every 30 minutes after the study begins, after the activity of the stable flies in their assigned cage has been verified, each pair of treated subjects will carefully put both their arms into the cage for 5 minutes. During the 5-minute exposure period we will count the number of stable flies (up to two) that bite the treated skin of either of your arms. When you receive two bites on the same arm in one exposure period, or one bite in each of two consecutive exposure periods, you will remove that arm from the cage and from the study. We will call this "breakdown", and once you reach breakdown on one of your arms you will no longer expose that arm for the rest of the day's study. You can then remove the bandages and tape from this arm, and scratch if you choose. Caladryl®, Calamine® lotion and rubbing alcohol will be provided to help stop any itching from bites you received. When you reach breakdown on both arms, you will have finished your part in the study and may go home.

12. After each 5-minute exposure period you may leave the test room, but you must remain in the lab. You can go to the restroom if you need to, and the Study Director will call breaks every few hours. You may either bring your own lunch or pay to have lunch ordered.

13. After preparation and treatment of subjects, which will take about one hour, the day's study will include up to 20 5-minute exposure periods at 30 minute intervals over 10 hours. The study will end after 10 hours or when all treated test subjects have reached breakdown on both arms, whichever comes first.

**Discomfort and Hazard**

**You will be exposed to two types of risk throughout the duration of this study.**

**Stable fly bites**

A bite occurs when a stable fly lands and sticks its pointed mouthparts into your skin and takes blood. A stable fly bite will cause momentary pain and

leave a small red mark which will usually disappear within a couple of days. The pain from a stable fly bites usually stops as soon as it stops biting. The irritation and swelling, which often result from mosquito bites, are not nearly so common after stable fly bites. In severe cases, a bite or probe may cause the development of large bumps on your skin, difficulty breathing, sweating and/or a rapid pulse. For some people this could be life-threatening.

All subjects will be exposed to stable flies for at least 1 minute to verify attractiveness to stable flies. Although we will try to brush the stable flies off before they bite, there is a slight possibility of being bitten.

Treated subjects will expose their forearms to stable flies for five minutes every half hour. Although they will not expose an arm further if they receive two bites on it in one exposure, or one bite in two consecutive exposure periods, they may receive more than two bites on each arm during the test. A bite which is not followed by another bite in the same or the next exposure will be disregarded. If you are a treated subject you will still need to receive at least two more bites on that arm to reach breakdown. The untreated control subject will be exposed to stable flies every half hour for up to one minute in each of six test cages. Although we will try to brush the landing stable flies off before they bite, the control subject is likely to be bitten by some of them. We will minimize the irritation from bites or probes you receive by making Caladryl® or Calamine® lotion or rubbing alcohol available at the study site for your use after the study is completed.

**Reaction to the test repellents**

You may have a reaction to the test repellents.

The Sponsor has minimized this possibility by choosing an active ingredient (picaridin) that has demonstrated low acute oral, skin, and inhalation toxicity. The Environmental Protection Agency (EPA) has classified it as low toxicity for acute inhalation toxicity and primary skin

irritation. EPA has classified the two test repellents as having low to mild toxicity based on eye irritation. For this reason it is important not to rub your eyes with your treated arms. The Sponsor has selected the non-repellent ingredients in the formulations because they are widely used in cosmetics and have a long history of safe use. ICR staff will be monitoring all subjects for any signs of a reaction to the test repellents. If you think you may be having such a reaction, tell a member of the staff immediately.

The stable flies being used in this study will be laboratory-reared and disease-free, and they will never have had a human blood meal. There is therefore no risk of your contracting any stable fly-borne disease as a result of participation in this study.

The temperature and humidity conditions present in the laboratory will be those maintained in a typical office environment and as such should be comfortable to most people.

Should you have any medical problems, we will have First- Aid- qualified staff members, and First- Aid- supplies on site. We will have cell phones to make emergency calls if necessary. In the case of medical emergency, we will transport you to a selected local hospital at our expense. We will pay all of your medical bills for study-related illnesses and injuries. The Principal Investigator will contact you by telephone, two weeks after the study to ask if you have experienced any adverse effects. You should contact the Principal Investigator any time after the study if you experience any study-related adverse effects, either before or after this follow up call.

**Financial Consideration**

We will pay you $11/hour for the first 9 hours and $17.50 for each additional hour that you spend on the day of the study. The study will last about 10 hours with an additional hour of prep time (11 hours total), with a total payment of $134 paid to you. This payment will be mailed to you on the 15th or the last day of the month. If we ask you to drop out of the test, and you have complied with all of our requests, you will still receive full payment. If we ask you to drop out of the test because you have not followed all of our directions, or if you choose to drop out of the test, we will compensate you for time up to that point at the rate of $11 per hour.

Test subject's initials:.....

Date:.....

**Costs**

There are no financial costs to you for participating in this study.

**Benefits**

You will get no personal benefit from participating in this study. The sponsor, LANXESS Corporation will gain the most direct benefit from the conduct of this study, which is expected to support additional marketing claims that these products repel stable flies.

Some benefit is also likely to result for society in general through showing the effectiveness of these products in repelling a potentially important public health pest.

**Your Rights**

We will give you an opportunity to discuss with us any aspects of this document or of the study it describes that are not clear to you, so that you fully understand the nature of the study, its purpose, and the procedures to be used, as well as the discomforts, and risks you may experience during or after the study. You are encouraged to ask questions at any time, before or after you consent to participate, and before, during, or after the study day itself. Your participation is entirely voluntary. You may decide not to take part in this study, and if you decide you would like to participate, you are free to change your mind at any time without having to explain, and without penalty or loss of benefits to which you may be otherwise entitled.

**Alternative**

The only alternative to participating is for you to decide not to.

Test subject's initials:.....

Date:.....

**Questions**

If you have any questions about this study or suffer a reaction you think might be associated with the study, call us at 410-747-4500. If you have any questions about your rights as a research participant, or related concerns, you may contact the Essex Institutional Review Board (IRB), 121 Main Street, Lebanon, NJ 08833, telephone 908-236-7735. The Essex IRB is a committee that has reviewed this research project to help ensure that the rights and welfare of the participants are protected and that the study is designed and carried out ethically. Review of this study by the Essex IRB is not an endorsement of the study or its outcome.

**Confidentiality**

We and the sponsor or its agents may use the information obtained from your taking part in this test, and this information may become part of a report. We will keep your participation as confidential as possible referring to you in the study data and reports only by your initials or an arbitrary ICR identification. However, we cannot guarantee that your identity will be kept confidential; the sponsor, personnel associated with the study, a regulatory agency such as the Environmental Protection Agency (EPA), and the Essex Institutional Review Board (EIRB) all have a right to review your records.

**Consent**

I voluntarily agree to participate in this study. I will be given a copy of this signed form. By signing this form I have not given up any of my legal rights.

_____

Signature of Subject Date Signature of Witness Date

_____

Signature of Principal Investigator Date

Test subject's initials:.....

Date:.....

# MATERIAL SAFETY DATA SHEET

LANXESS
Energizing Chemistry

**LANXESS Corporation**
**Product Safety & Regulatory Affairs**
**111 RIDC Park West Drive**
**Pittsburgh, PA 15275-1112**
**USA**

**TRANSPORTATION EMERGENCY**

| | |
|---|---|
| CALL CHEMTREC: | (800) 424-9300 |
| INTERNATIONAL: | (703) 527-3887 |

**NON-TRANSPORTATION**

| | |
|---|---|
| LANXESS Emergency Phone: | (800) 410-3063 |
| LANXESS Information Phone: | (800) LANXESS |

## 1. Product and Company Identification

| | |
|---|---|
| **Product Name:** | KBR 3023 ALL-FAM.INSECT REPELL.CREAM MUS |
| **Material Number:** | 56154780 |
| **Chemical Name:** | Formulation containing Hydroxyethyl Butyl Piperidine Carboxylate (Picaridin) |

## 2. Hazards Identification

**Emergency Overview**

**WARNING! Color:** Colorless to light yellow **Form:** liquid Cream **Odor:** Slight, Alcohol.
Flammable. Vapors may spread long distances and ignite. Vapors or mist may be a fire and explosion hazard when exposed to high temperature or ignition. Use cold water spray to cool fire-exposed containers to minimize the risk of rupture. Inhalation may cause nausea or dizziness. May cause respiratory tract irritation. Causes eye irritation.

**Potential Health Effects**

| | |
|---|---|
| **Primary Routes of Entry:** | Skin Contact, Eye Contact, Ingestion, Inhalation |
| **Medical Conditions Aggravated by Exposure:** | Skin disorders, Respiratory disorders, Eye disorders |

**HUMAN EFFECTS AND SYMPTOMS OF OVEREXPOSURE**

**Inhalation**
**Acute Inhalation**
**For Component: Ethanol**
May cause nervous system effects which can include symptoms of dizziness, incoordination, headache, numbness, and/or confusion. May cause respiratory tract irritation with symptoms of coughing, sore throat and runny nose.

**For Component: Glycerin**

Inhalation is unlikely due to the low vapor pressure. If misted or handled at elevated temperatures, high concentrations may cause respiratory tract irritation.

**Chronic Inhalation**
**For Component: Ethanol**
Chronic exposure to organic solvents has been associated with various neurotoxic effects including permanent brain and nervous system damage.

**Skin**
**Acute Skin**
**For Product: KBR 3023 ALL-FAM.INSECT REPELL.CREAM MUS**
May cause slight irritation.

**For Component: Ethanol**
May cause slight irritation.

**For Component: Glycerin**
Not expected to be irritating. Not expected to be a skin sensitizer.

**Eye**
**Acute Eye**
**For Component: Ethanol**
Causes irritation with symptoms of reddening, tearing, stinging, and swelling.

**For Component: Glycerin**
May cause slight irritation.

**Ingestion**
**Acute Ingestion**
**For Component: Ethanol**
May cause nervous system effects which can include symptoms of dizziness, incoordination, headache, numbness, and/or confusion.

**For Component: Glycerin**
Not expected to be harmful if swallowed.

**Chronic Ingestion**
**For Component: Ethanol**
Chronic exposure to organic solvents has been associated with various neurotoxic effects including permanent brain and nervous system damage.

**General Effects of Exposure**
**Chronic Effects of Exposure**
**For Product: KBR 3023 ALL-FAM.INSECT REPELL.CREAM MUS**
Chronic exposure to organic solvents has been associated with various neurotoxic effects including permanent brain and nervous system damage.

**Carcinogenicity:**
No Carcinogenic substances as defined by IARC, NTP and/or OSHA.

## 3. Composition/Information on Ingredients

**Hazardous Components**

| Weight % | Components | CAS-No. |
|---|---|---|

| | | |
|---|---|---|
| 5 - 10% | Ethanol | 64-17-5 |
| 3 - 7% | Glycerin | 56-81-5 |

## 4. First Aid Measures

**Eye Contact**
In case of contact, flush eyes with plenty of lukewarm water. Get medical attention if irritation develops.

**Skin Contact**
Discontinue use and contact a physician if skin sensitivity or irritation develops. Get medical attention if irritation develops.

**Inhalation**
If inhaled, remove to fresh air. Get medical attention if irritation develops.

**Ingestion**
If ingested, do not induce vomiting unless directed to do so by medical personnel. Get medical attention.

## 5. Fire-Fighting Measures

**Suitable Extinguishing Media:** All extinguishing media are suitable.

**Special Fire Fighting Procedures**
Firefighters should be equipped with self-contained breathing apparatus to protect against potentially toxic and irritating fumes. Use cold water spray to cool fire-exposed containers to minimize risk of rupture.

**Unusual Fire/Explosion Hazards**
Flammable Liquid. Vapors may spread long distances and ignite. Vapors or mist may be a fire and explosion hazard when exposed to high temperature or ignition. Toxic and irritating gases/fumes may be given off during burning or thermal decomposition.

## 6. Accidental release measures

**Spill and Leak Procedures**
Cleanup personnel must use appropriate personal protective equipment. Cover spill with inert material (e. g., dry sand or earth) and collect for proper disposal. Remove all sources of ignition, including flames, heat, and sparks.

## 7. Handling and Storage

**Handling/Storage Precautions**
Keep away from heat, sparks and open flames. Ground and bond containers and equipment before transferring to avoid static sparks. Avoid breathing dust, vapor, or mist. Avoid contact with skin or clothing. Avoid contact with eyes. Use only with adequate ventilation/personal protection. Wash thoroughly after handling. Keep container closed when not in use.

## 8. Exposure Controls / Personal Protection

**Ethanol (64-17-5)**

US. ACGIH Threshold Limit Values
Time Weighted Average (TWA): 1,000 ppm
US. OSHA Table Z-1 Limits for Air Contaminants (29 CFR 1910.1000)
PEL: 1,000 ppm, 1,900 mg/m3
US. ACGIH Threshold Limit Values
Hazard Designation: Group A4 Not classifiable as a human carcinogen.

**Glycerin (56-81-5)**

US. ACGIH Threshold Limit Values
Time Weighted Average (TWA): 10 mg/m3 (Mist.)
US. OSHA Table Z-1 Limits for Air Contaminants (29 CFR 1910.1000)
PEL: 5 mg/m3 (Respirable fraction.)
US. OSHA Table Z-1 Limits for Air Contaminants (29 CFR 1910.1000)
PEL: 15 mg/m3 (Total dust.)

**Industrial Hygiene/Ventilation Measures**
General dilution and local exhaust as necessary to control airborne vapors, mists, dusts and thermal decomposition products below appropriate airborne concentration standards/guidelines.

**Respiratory Protection**
None required under normal conditions of use.

**Hand Protection**
No gloves required during normal handling and use.

**Eye Protection**
safety glasses.

**Skin and body protection**
Wear cloth work clothing including long pants and long-sleeved shirts.

**Additional Protective Measures**
Employees should wash their hands and face before eating, drinking, or using tobacco products. Educate and train employees in the safe use and handling of this product. Emergency showers and eye wash stations should be available.

## 9. Physical and chemical properties

| | |
|---|---|
| **Form:** | liquid |
| **Appearance:** | Cream |
| **Color:** | Colorless to light yellow |
| **Odor:** | Slight, Alcohol |
| **pH:** | Not Established |
| **Boiling Point/Range:** | > 35 °C (> 95 °F) |
| **Flash Point:** | 23 - 61 °C (73.4 - 141.8 °F) |
| **Vapor Pressure:** | < 1,100 hPa @ 20 °C (68 °F) |
| **Density:** | 0.98 - 1 g/cm3 |
| **Solubility in Water:** | Soluble |

## 10. Stability and Reactivity

**Hazardous Reactions**
Hazardous polymerization does not occur.

**Stability**
Stable

**Materials to avoid**
Oxidizing agents

**Conditions to avoid**
Heat, flames and sparks.

**Hazardous decomposition products**
By Fire and Thermal Decomposition: Thermal decomposition may produce CO, CO2, and other potentially toxic fumes., nitrogen oxides (NOx)

## 11. Toxicological Information

**Toxicity Data for 1-Piperidinecarboxylic Acid, 2-(2-hydroxyethyl)-, 1-methylpropylester**
**Acute Oral Toxicity**
LD50: 2,236 mg/kg (Rat)

**Acute Inhalation Toxicity**
LC50: 4,364 mg/l, aerosol, 4 h (rat)

**Acute dermal toxicity**
LD50: > 2,000 mg/kg (rabbit)

**Skin Irritation**
rabbit, Non-irritating

**Eye Irritation**
rabbit, Slightly irritating

**Sensitization**
Buehler Test: non-sensitizer (Guinea pig)

**Mutagenicity**
Genetic Toxicity in Vitro:
Ames: negative
Genetic Toxicity in Vivo:
Micronucleus Assay: negative (mouse)

**Toxicity Data for Ethanol**
**Acute Oral Toxicity**
LD50: > 5,000 mg/kg (Rat)

**Acute Inhalation Toxicity**
LC50: 5.9 mg/l, 6 hrs (Rat)
LC50: 124.7 mg/l, 4 hrs (Rat)
LC50: 20000 ppm, 10 h (Rat)

**Skin Irritation**

rabbit, Draize, Exposure Time: 24 hrs, Moderately irritating
rabbit, OECD Guideline for Testing of Chemicals, No. 404, Non-irritating

**Eye Irritation**
rabbit, Draize, Severely irritating

**Sensitization**
dermal: non-sensitizer (Guinea pig, Maximization Test)

**Repeated Dose Toxicity**
84 Days, oral: NOAEL: 10 g/kg, (Rat)
There were no adverse effects seen at highest dose tested.
74 Days, inhalation: NOAEL: 3000 ppm, (Guinea pig)
There were no adverse effects seen at highest dose tested.

**Mutagenicity**
Genetic Toxicity in Vitro:
Ames: negative (Salmonella typhimurium, Metabolic Activation: with/without)
Genetic Toxicity in Vivo:

Positive and negative results were seen in various in vitro and in vivo studies.

**Carcinogenicity**
Rat, Male/Female, oral, 2 Years,
negative

**Toxicity to Reproduction/Fertility**
Reproductive effects have been observed in animal studies.

**Developmental Toxicity/Teratogenicity**
Fetotoxicity has been observed in animal studies. Teratogenic effects have been observed in animal studies.

**Toxicity Data for Glycerin**
**Acute Oral Toxicity**
LD50: > 5,000 mg/kg (Rat)

**Skin Irritation**
rabbit, Non-irritating

**Eye Irritation**
rabbit, Slightly irritating

**Sensitization**
dermal: non-sensitizer (Human, Patch Test)

**Repeated Dose Toxicity**
90 Days, inhalation: NOAEL: 0.167 mg/l, (Rat)

**Mutagenicity**
Genetic Toxicity in Vitro:
Ames: negative (Salmonella typhimurium, Metabolic Activation: with/without)

## 12. Ecological Information

**Ecological Data for 1-Piperidinecarboxylic Acid, 2-(2-hydroxyethyl)-, 1-methylpropylester**

**Acute and Prolonged Toxicity to Fish**
LC50: 173 mg/l (Rainbow (Donaldson)Trout (Oncorhynchus mykiss), 96 h)
NOEC: 3.19 mg/l (Zebra fish (Brachydanio rerio), 768 h)

**Acute Toxicity to Aquatic Invertebrates**
EC50: > 100 mg/l (Water flea (Daphnia magna), 48 h)

**Toxicity to Microorganisms**
EC50: 1,100 mg/l,

**Ecological Data for Ethanol**

**Biodegradation**
Aerobic, 84 %, Exposure time: 20 Days
Readily biodegradable.

**Chemical Oxygen Demand (COD)**
1,700 mg/g

**Acute and Prolonged Toxicity to Fish**
LC50: 14,200 mg/l (Fathead minnow (Pimephales promelas), 96 hrs)
LC50: 8,140 mg/l (Golden orfe (Leuciscus idus), 48 hrs)

**Acute Toxicity to Aquatic Invertebrates**
EC50: 10,800 mg/l (Water flea (Daphnia magna), 24 hrs)

**Toxicity to Aquatic Plants**
EC50: 9,310 mg/l, End Point: growth (Green algae (Chlorella pyrenoidosa))

**Ecological Data for Glycerin**

**Biodegradation**
Aerobic, 63 %, Exposure time: 14 Days
Readily biodegradable.

**Biological Oxygen Demand (BOD)**
5 Days, 700 mg/l

**Chemical Oxygen Demand (COD)**
1,150 mg/g

**Acute and Prolonged Toxicity to Fish**
LC0: > 10,000 mg/l (Golden orfe (Leuciscus idus), 48 hrs)

**Acute Toxicity to Aquatic Invertebrates**
EC50: > 10,000 mg/l (Water flea (Daphnia magna), 24 hrs)

## 13. Disposal considerations

**Waste Disposal Method**
Waste disposal should be in accordance with existing federal, state and local environmental control laws.

**Empty Container Precautions**
Do not heat or cut container with electric or gas torch. Recondition or dispose of empty container in accordance with governmental regulations. Do not reuse empty container without proper cleaning. Label

precautions also apply to this container when empty.

## 14. Transportation information

**Land transport (DOT)**

| | |
|---|---|
| **Proper Shipping Name:** | Flammable liquids, n.o.s. (contains Ethanol) |
| **Hazard Class or Division:** | 3 |
| **UN/NA Number:** | UN1993 |
| **Packaging Group:** | III |
| **Hazard Label(s):** | Flammable Liquid |

**Sea transport (IMDG)**

| | |
|---|---|
| **Proper Shipping Name:** | FLAMMABLE LIQUID, N.O.S. (contains Ethanol) |
| **Hazard Class or Division:** | 3 |
| **UN-No:** | UN1993 |
| **Packaging Group:** | III |
| **Hazard Label(s):** | Flammable liquids |

**Air transport (ICAO/IATA)**

| | |
|---|---|
| **Proper Shipping Name:** | Flammable liquid, n.o.s. (contains Ethanol) |
| **Hazard Class or Division:** | 3 |
| **UN-No:** | UN1993 |
| **Packaging Group:** | III |
| **Hazard Label(s):** | Flammable liquids |

## 15. Regulatory Information

**United States Federal Regulations**

**OSHA Hazcom Standard Rating:** Hazardous

**US. Toxic Substances Control Act:** Not listed on TSCA Inventory, for R&D Use Only, Section 5 (h)(3) limitations apply.

**US. EPA CERCLA Hazardous Substances (40 CFR 302):**
**Components**
None

**SARA Section 311/312 Hazard Categories:**
Acute Health Hazard, Fire Hazard

**US. EPA Emergency Planning and Community Right-To-Know Act (EPCRA) SARA Title III Section 302 Extremely Hazardous Substance (40 CFR 355, Appendix A):**
**Components**
None

**US. EPA Emergency Planning and Community Right-To-Know Act (EPCRA) SARA Title III Section 313 Toxic Chemicals (40 CFR 372.65) - Supplier Notification Required:**
**Components**
None

**US. EPA Resource Conservation and Recovery Act (RCRA) Composite List of Hazardous Wastes and Appendix VIII Hazardous Constituents (40 CFR 261):**
When discarded in its purchased form, this product meets the criteria of ignitability, and should be managed as a hazardous waste (EPA Hazardous Waste Number D001). (40 CFR 261.20-24)

**State Right-To-Know Information**
The following chemicals are specifically listed by individual states; other product specific health and safety data in other sections of the MSDS may also be applicable for state requirements. For details on your regulatory requirements you should contact the appropriate agency in your state.

**Massachusetts, New Jersey or Pennsylvania Right to Know Substance Lists:**

| Weight % | Components | CAS-No. |
|---|---|---|
| >=1% | Water | 7732-18-5 |
| >=1% | 1-Piperidinecarboxylic Acid, 2-(2-hydroxyethyl)-, 1-methylpropylester | 119515-38-7 |
| 5 - 10% | Ethanol | 64-17-5 |
| 3 - 7% | Glycerin | 56-81-5 |
| >=1% | 1H-Benzimidazole-6,3'-Disulfonic acid, 2-Octadecyl-1-(Phenylmethyl)-, Sodium salt | 187230-40-6 |

**New Jersey Environmental Hazardous Substances List and/or New Jersey RTK Special Hazardous Substances Lists:**

| Weight % | Components | CAS-No. |
|---|---|---|
| 5 - 10% | Ethanol | 64-17-5 |

**California Prop. 65:**
To the best of our knowledge, this product does not contain any of the listed chemicals, which the state of California has found to cause cancer, birth defects or other reproductive harm.

## 16. Other Information

**NFPA 704M Rating**

| | |
|---|---|
| **Health** | 1 |
| **Flammability** | 3 |
| **Reactivity** | 0 |
| **Other** | |

0=Insignificant 1=Slight 2=Moderate 3=High 4=Extreme

**HMIS Rating**

| | |
|---|---|
| **Health** | 1 |
| **Flammability** | 3 |
| **Physical Hazard** | 0 |

0=Minimal 1=Slight 2=Moderate 3=Serious 4=Severe
* = Chronic Health Hazard

LANXESS Corporation's method of hazard communication is comprised of Product Labels and Material Safety Data Sheets. HMIS and NFPA ratings are provided by LANXESS Corporation as a customer service.

| | |
|---|---|
| Contact Person: | Product Safety Department |
| Telephone: | (800) LANXESS |
| MSDS Number: | 000000005990 |
| Version Date: | 06/09/2006 |
| Report Version: | 1.0 |

This information is furnished without warranty, express or implied. This information is believed to be accurate to the best knowledge of LANXESS Corporation. The information in this MSDS relates only to the specific material designated herein. LANXESS Corporation assumes no legal responsibility for use of or reliance upon the information in this MSDS.

# MATERIAL SAFETY DATA SHEET

LANXESS
Energizing Chemistry

**LANXESS Corporation**
**Product Safety & Regulatory Affairs**
**111 RIDC Park West Drive**
**Pittsburgh, PA 15275-1112**
**USA**

**TRANSPORTATION EMERGENCY**

| | |
|---|---|
| CALL CHEMTREC: | (800) 424-9300 |
| INTERNATIONAL: | (703) 527-3887 |

**NON-TRANSPORTATION**

| | |
|---|---|
| LANXESS Emergency Phone: | (800) 410-3063 |
| LANXESS Information Phone: | (800) LANXESS |

## 1. Product and Company Identification

| | |
|---|---|
| **Product Name:** | KBR 3023 ALL-FAMILY INSECT REPELLENT SPRAY |
| **Material Number:** | 56115181 |
| **Chemical Name:** | Formulation containing Hydroxyethyl Butyl Piperidine Carboxylate (Picaridin) |
| **Synonyms:** | Formulation containing 1-Piperidinecarboxylic acid, 2-(2-hydroxyethyl)-, 1-methylpropyl-ester |

## 2. Hazards Identification

**Emergency Overview**

**WARNING! Color:** Colorless to light yellow **Form:** liquid **Odor:** Slight, Alcohol. Flammable. Vapors may spread long distances and ignite. Vapors or mist may be a fire and explosion hazard when exposed to high temperature or ignition. Use cold water spray to cool fire-exposed containers to minimize the risk of rupture. Inhalation may cause nausea or dizziness. May cause respiratory tract irritation. Causes eye irritation.

**Potential Health Effects**

| | |
|---|---|
| **Primary Routes of Entry:** | Skin Contact, Eye Contact, Ingestion, Inhalation |
| **Medical Conditions Aggravated by Exposure:** | Skin disorders, Respiratory disorders, Eye disorders |

**HUMAN EFFECTS AND SYMPTOMS OF OVEREXPOSURE**

**Inhalation**
**Acute Inhalation**
**For Component: Ethanol**
May cause nervous system effects which can include symptoms of dizziness, incoordination, headache, numbness, and/or confusion. May cause respiratory tract irritation with symptoms of coughing, sore throat and runny nose.

**Chronic Inhalation**
**For Component: Ethanol**
Chronic exposure to organic solvents has been associated with various neurotoxic effects including permanent brain and nervous system damage.

**Skin**
**Acute Skin**
**For Product: KBR 3023 ALL-FAMILY INSECT REPELLENT SPRAY**
May cause slight irritation.

**For Component: Ethanol**
May cause slight irritation.

**Eye**
**Acute Eye**
**For Component: Ethanol**
Causes irritation with symptoms of reddening, tearing, stinging, and swelling.

**Ingestion**
**Acute Ingestion**
**For Component: Ethanol**
May cause nervous system effects which can include symptoms of dizziness, incoordination, headache, numbness, and/or confusion.

**Chronic Ingestion**
**For Component: Ethanol**
Chronic exposure to organic solvents has been associated with various neurotoxic effects including permanent brain and nervous system damage.

**General Effects of Exposure**
**Chronic Effects of Exposure**
**For Product: KBR 3023 ALL-FAMILY INSECT REPELLENT SPRAY**
Chronic exposure to organic solvents has been associated with various neurotoxic effects including permanent brain and nervous system damage.

**Carcinogenicity:**
No Carcinogenic substances as defined by IARC, NTP and/or OSHA.

## 3. Composition/Information on Ingredients

**Hazardous Components**

| Weight % | Components | CAS-No. |
|---|---|---|
| 25 - 35% | Ethanol | 64-17-5 |

## 4. First Aid Measures

**Eye Contact**
In case of contact, flush eyes with plenty of lukewarm water. Get medical attention if irritation develops.

**Skin Contact**
In case of skin contact, wash affected areas with soap and water. Immediately remove contaminated clothing and shoes. Get medical attention if irritation develops.

**Inhalation**
If inhaled, remove to fresh air. Get medical attention if irritation develops.

**Ingestion**
If ingested, do not induce vomiting unless directed to do so by medical personnel. Get medical attention.

## 5. Fire-Fighting Measures

**Suitable Extinguishing Media:** All extinguishing media are suitable.

**Special Fire Fighting Procedures**
Firefighters should be equipped with self-contained breathing apparatus to protect against potentially toxic and irritating fumes. Use cold water spray to cool fire-exposed containers to minimize risk of rupture.

**Unusual Fire/Explosion Hazards**
Flammable Liquid. Vapors may spread long distances and ignite. Vapors or mist may be a fire and explosion hazard when exposed to high temperature or ignition. Toxic and irritating gases/fumes may be given off during burning or thermal decomposition.

## 6. Accidental release measures

**Spill and Leak Procedures**
Cleanup personnel must use appropriate personal protective equipment. Cover spill with inert material (e. g., dry sand or earth) and collect for proper disposal. Remove all sources of ignition, including flames, heat, and sparks.

## 7. Handling and Storage

**Handling/Storage Precautions**
Keep away from heat, sparks and open flames. Ground and bond containers and equipment before transferring to avoid static sparks. Avoid breathing dust, vapor, or mist. Avoid contact with skin or clothing. Avoid contact with eyes. Use only with adequate ventilation/personal protection. Wash thoroughly after handling. Keep container closed when not in use.

## 8. Exposure Controls / Personal Protection

**Ethanol (64-17-5)**
US. ACGIH Threshold Limit Values
Time Weighted Average (TWA): 1,000 ppm
US. OSHA Table Z-1 Limits for Air Contaminants (29 CFR 1910.1000)
PEL: 1,000 ppm, 1,900 mg/m3
US. ACGIH Threshold Limit Values
Hazard Designation: Group A4 Not classifiable as a human carcinogen.

**Industrial Hygiene/Ventilation Measures**

General dilution and local exhaust as necessary to control airborne vapors, mists, dusts and thermal decomposition products below appropriate airborne concentration standards/guidelines.

**Respiratory Protection**
In case of insufficient ventilation wear suitable respiratory equipment., NIOSH approved, air-purifying organic vapor respirator.

**Hand Protection**
Permeation resistant gloves.

**Eye Protection**
safety glasses with side-shields.

**Skin and body protection**
Wear cloth work clothing including long pants and long-sleeved shirts.

**Additional Protective Measures**
Employees should wash their hands and face before eating, drinking, or using tobacco products. Educate and train employees in the safe use and handling of this product. Emergency showers and eye wash stations should be available.

## 9. Physical and chemical properties

| | |
|---|---|
| **Form:** | liquid |
| **Color:** | Colorless to light yellow |
| **Odor:** | Slight, Alcohol |
| **pH:** | Not Established |
| **Boiling Point/Range:** | > 35 °C (> 95 °F) |
| **Flash Point:** | 26 °C (78.8 °F) |
| **Solubility in Water:** | Soluble |

## 10. Stability and Reactivity

**Hazardous Reactions**
Hazardous polymerization does not occur.

**Stability**
Stable

**Materials to avoid**
Oxidizing agents

**Conditions to avoid**
Heat, flames and sparks.

**Hazardous decomposition products**
By Fire and Thermal Decomposition: Thermal decomposition may produce CO, CO2, and other potentially toxic fumes., nitrogen oxides (NOx)

## 11. Toxicological Information

**Toxicity Data for 1-Piperidinecarboxylic Acid, 2-(2-hydroxyethyl)-, 1-methylpropylester**

**Acute Oral Toxicity**
LD50: 2,236 mg/kg (Rat)

**Acute Inhalation Toxicity**
LC50: 4,364 mg/l, aerosol, 4 h (rat)

**Acute dermal toxicity**
LD50: > 2,000 mg/kg (rabbit)

**Skin Irritation**
rabbit, Non-irritating

**Eye Irritation**
rabbit, Slightly irritating

**Sensitization**
Buehler Test: non-sensitizer (Guinea pig)

**Mutagenicity**
Genetic Toxicity in Vitro:
Ames: negative
Genetic Toxicity in Vivo:
Micronucleus Assay: negative (mouse)

**Toxicity Data for Ethanol**
**Acute Oral Toxicity**
LD50: > 5,000 mg/kg (Rat)

**Acute Inhalation Toxicity**
LC50: 5.9 mg/l, 6 hrs (Rat)
LC50: 124.7 mg/l, 4 hrs (Rat)
LC50: 20000 ppm, 10 h (Rat)

**Skin Irritation**
rabbit, Draize, Exposure Time: 24 hrs, Moderately irritating
rabbit, OECD Guideline for Testing of Chemicals, No. 404, Non-irritating

**Eye Irritation**
rabbit, Draize, Severely irritating

**Sensitization**
dermal: non-sensitizer (Guinea pig, Maximization Test)

**Repeated Dose Toxicity**
84 Days, oral: NOAEL: 10 g/kg, (Rat)
There were no adverse effects seen at highest dose tested.
74 Days, inhalation: NOAEL: 3000 ppm, (Guinea pig)
There were no adverse effects seen at highest dose tested.

**Mutagenicity**
Genetic Toxicity in Vitro:
Ames: negative (Salmonella typhimurium, Metabolic Activation: with/without)
Genetic Toxicity in Vivo:

Positive and negative results were seen in various in vitro and in vivo studies.

**Carcinogenicity**

Rat, Male/Female, oral, 2 Years,
negative

**Toxicity to Reproduction/Fertility**
Reproductive effects have been observed in animal studies.

**Developmental Toxicity/Teratogenicity**
Fetotoxicity has been observed in animal studies. Teratogenic effects have been observed in animal studies.

**Toxicity Data for Polyethylene Glycol**
**Acute Oral Toxicity**
LD50: > 5,000 mg/kg (Rat)

**Acute Inhalation Toxicity**
LC0: 2516 mg/m3, 6 hrs (Rat)

**Acute dermal toxicity**
LD50: > 5,000 mg/kg (rabbit)

**Eye Irritation**
rabbit, No eye irritation

**Mutagenicity**
Genetic Toxicity in Vitro:
Ames: negative
Genetic Toxicity in Vivo:
negative (Drosophila melanogaster, )

**Developmental Toxicity/Teratogenicity**
rat, female, oral, gestation, NOAEL (teratogenicity): 10,000 mg/kg,
No Teratogenic effects observed at doses tested.

## 12. Ecological Information

**Ecological Data for 1-Piperidinecarboxylic Acid, 2-(2-hydroxyethyl)-, 1-methylpropylester**
**Acute and Prolonged Toxicity to Fish**
LC50: 173 mg/l (Rainbow (Donaldson)Trout (Oncorhynchus mykiss), 96 h)
NOEC: 3.19 mg/l (Zebra fish (Brachydanio rerio), 768 h)

**Acute Toxicity to Aquatic Invertebrates**
EC50: > 100 mg/l (Water flea (Daphnia magna), 48 h)

**Toxicity to Microorganisms**
EC50: 1,100 mg/l,

**Ecological Data for Ethanol**
**Biodegradation**
Aerobic, 84 %, Exposure time: 20 Days
Readily biodegradable.

**Chemical Oxygen Demand (COD)**
1,700 mg/g

**Acute and Prolonged Toxicity to Fish**

LC50: 14,200 mg/l (Fathead minnow (Pimephales promelas), 96 hrs)
LC50: 8,140 mg/l (Golden orfe (Leuciscus idus), 48 hrs)

**Acute Toxicity to Aquatic Invertebrates**
EC50: 10,800 mg/l (Water flea (Daphnia magna), 24 hrs)

**Toxicity to Aquatic Plants**
EC50: 9,310 mg/l, End Point: growth (Green algae (Chlorella pyrenoidosa))

**Ecological Data for Polyethylene Glycol**
**Biological Oxygen Demand (BOD)**
5 Days, 6 %
20 Days, 77 %

**Chemical Oxygen Demand (COD)**
1.84 mg/g

**Acute and Prolonged Toxicity to Fish**
LC50: > 10,000 mg/l (Fathead minnow (Pimephales promelas), 96 hrs)

**Acute Toxicity to Aquatic Invertebrates**
EC50: > 10,000 mg/l (Water flea (Daphnia magna), 48 hrs)

**Toxicity to Microorganisms**
> 5,000 mg/l, (16 hrs)

## 13. Disposal considerations

**Waste Disposal Method**
Waste disposal should be in accordance with existing federal, state and local environmental control laws.

**Empty Container Precautions**
Do not heat or cut container with electric or gas torch. Recondition or dispose of empty container in accordance with governmental regulations. Do not reuse empty container without proper cleaning. Label precautions also apply to this container when empty.

## 14. Transportation information

**Land transport (DOT)**

| | |
|---|---|
| **Proper Shipping Name:** | Flammable liquids, n.o.s. (contains Ethanol) |
| **Hazard Class or Division:** | 3 |
| **UN/NA Number:** | UN1993 |
| **Packaging Group:** | III |
| **Hazard Label(s):** | Flammable Liquid |

**Sea transport (IMDG)**

| | |
|---|---|
| **Proper Shipping Name:** | FLAMMABLE LIQUID, N.O.S. (contains Ethanol) |
| **Hazard Class or Division:** | 3 |
| **UN-No:** | UN1993 |
| **Packaging Group:** | III |
| **Hazard Label(s):** | Flammable liquids |

**Air transport (ICAO/IATA)**

| | |
|---|---|
| **Proper Shipping Name:** | Flammable liquid, n.o.s. (contains Ethanol) |
| **Hazard Class or Division:** | 3 |
| **UN-No:** | UN1993 |
| **Packaging Group:** | III |
| **Hazard Label(s):** | Flammable liquids |

## 15. Regulatory Information

**United States Federal Regulations**

**OSHA Hazcom Standard Rating:** Hazardous

**US. Toxic Substances Control Act:** Not listed on TSCA Inventory, for R&D Use Only, Section 5 (h)(3) limitations apply.

**US. EPA CERCLA Hazardous Substances (40 CFR 302):**
**Components**
None

**SARA Section 311/312 Hazard Categories:**
Acute Health Hazard, Fire Hazard

**US. EPA Emergency Planning and Community Right-To-Know Act (EPCRA) SARA Title III Section 302 Extremely Hazardous Substance (40 CFR 355, Appendix A):**
**Components**
None

**US. EPA Emergency Planning and Community Right-To-Know Act (EPCRA) SARA Title III Section 313 Toxic Chemicals (40 CFR 372.65) - Supplier Notification Required:**
**Components**
None

**US. EPA Resource Conservation and Recovery Act (RCRA) Composite List of Hazardous Wastes and Appendix VIII Hazardous Constituents (40 CFR 261):**
When discarded in its purchased form, this product meets the criteria of ignitability, and should be managed as a hazardous waste (EPA Hazardous Waste Number D001). (40 CFR 261.20-24)

**State Right-To-Know Information**
The following chemicals are specifically listed by individual states; other product specific health and safety data in other sections of the MSDS may also be applicable for state requirements. For details on your regulatory requirements you should contact the appropriate agency in your state.

**Massachusetts, New Jersey or Pennsylvania Right to Know Substance Lists:**

| Weight % | Components | CAS-No. |
|---|---|---|
| >=1% | Water | 7732-18-5 |
| 25 - 35% | Ethanol | 64-17-5 |
| >=1% | Polyethylene Glycol | 25322-68-3 |
| >=1% | 1-Piperidinecarboxylic Acid, 2-(2-hydroxyethyl)-, 1-methylpropylester | 119515-38-7 |
| >=1% | Proprietary Non-Hazardous Ingredients | |

**New Jersey Environmental Hazardous Substances List and/or New Jersey RTK Special Hazardous Substances Lists:**

| Weight % | Components | CAS-No. |
|---|---|---|
| 25 - 35% | Ethanol | 64-17-5 |

**California Prop. 65:**
To the best of our knowledge, this product does not contain any of the listed chemicals, which the state of California has found to cause cancer, birth defects or other reproductive harm.

## 16. Other Information

**NFPA 704M Rating**

| | |
|---|---|
| **Health** | 1 |
| **Flammability** | 3 |
| **Reactivity** | 0 |
| **Other** | |

0=Insignificant 1=Slight 2=Moderate 3=High 4=Extreme

**HMIS Rating**

| | |
|---|---|
| **Health** | 1 |
| **Flammability** | 3 |
| **Physical Hazard** | 0 |

0=Minimal 1=Slight 2=Moderate 3=Serious 4=Severe
* = Chronic Health Hazard

LANXESS Corporation's method of hazard communication is comprised of Product Labels and Material Safety Data Sheets. HMIS and NFPA ratings are provided by LANXESS Corporation as a customer service.

| | |
|---|---|
| Contact Person: | Product Safety Department |
| Telephone: | (800) LANXESS |
| MSDS Number: | 000000005791 |
| Version Date: | 03/15/2006 |
| Report Version: | 1.0 |

This information is furnished without warranty, express or implied. This information is believed to be accurate to the best knowledge of LANXESS Corporation. The information in this MSDS relates only to the specific material designated herein. LANXESS Corporation assumes no legal responsibility for use of or reliance upon the information in this MSDS.

ICR | *Independent Laboratory*
*Pesticide Efficacy Testing*
*Regulatory Services*

January 24, 2008

Glenn P. Lambert, MD, FAAP
Chairman
Essex Institutional Review Board, Inc
121 Main Street
Lebanon, NJ 08833

Dear Dr. Lambert:

Please find enclosed the signed original indemnifications for Protocol # G4330108001A382, entitled *"Evaluation of the Efficacy of KBR 3023 (Picaridin; Icaridin)-Based Personal Insect Repellents (20% Cream and 20% Spray) Against Stable Flies in the Laboratory:*

1. Three signed EIRB indemnifications for LANXESS
2. One ICR indemnification signed by both parties

All the other documents associated with this protocol were sent on Wednesday 23th to be delivered on Thursday 24th.

Please do not hesitate to contact us if you should have questions.

Sincerely,

Robin G. Todd, PhD BCE
Director

enclosures



1330 Dillon Heights Avenue, Baltimore, MD 21228-1199 | **tel** 410.747.4500 | **fax** 410.747.4928 | **web** www.icrlab.com

**INDEMNIFICATION AGREEMENT**
Between
LANXESS Corporation
[Company Name]
and
ESSEX INSTITUTIONAL REVIEW BOARD, INC.

LANXESS Corporation (hereafter "LANXESS") agrees to hold harmless, Essex Institutional Review Board, its principals, agents and board members ("EIRB") from any claims of injury or illness resulting from the evaluation and implementation of Protocol, #G4330108001A382, entitled "EVALUATION OF THE EFFICACY OF KBR 3023 (Picaridin; Icaridin)-BASED PERSONAL INSECT REPELLENTS (20% CREAM and 20% SPRAY) AGAINST STABLE FLIES IN THE LABORATORY" under the following circumstances:

If any undesirable side effect or reaction occurs following the administration of the product and if EIRB has employed reasonable care in the evaluation of the protocol, and has not violated any local, state, or federal laws, pertaining to medical devices, drugs or biological agents, including but not limited to, the Federal Food, Drug and Cosmetic Act of 1938, as amended, and the regulations promulgated pursuant thereto, LANXESS shall indemnify and hold harmless EIRB against any and all claims, lawsuits, and judgments thereon (including reasonable attorney fees through the appellate level), which may be brought against them as a result of the evaluation or implementation of the protocol.

In the event any such claim is made or lawsuit is initiated, EIRB shall give prompt written notice thereof to LANXESS, shall permit LANXESS, or its insurance carrier, to defend such claim or lawsuit and shall cooperate fully in any such defense.

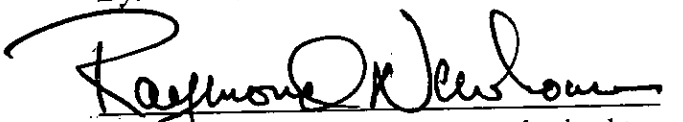
Essex Institutional Review Board
Accepted By:

_____
[Signature of person authorized to legally bind]

_____
[Printed Name of person authorized to to legally bind]

_____
Date

[Company Name] LANXESS Corp.
By:



[Signature of Company person authorized to to legally bind]

Raymond Newhouse, Chief Financial Officer
[Printed Name of Company person authorized to legally bind]

Date

Version Date: January 31, 2007

**Indemnification Agreement**
**Between**

**LANXESS CORPORATION**
**and**
**ICR, INC.**

**LANXESS Corporation** ("LANXESS") agrees to hold harmless **ICR, Inc.** ("**ICR**") from any claims of injury or illness resulting from the development, evaluation and implementation of Protocol No.G4330108001A382, entitled EVALUATION OF THE EFFICACY OF KBR 3023 (Picaridin; Icaridin)- BASED PERSONAL INSECT REPELLENTS (20% CREAM and 20% SPRAY) AGAINST STABLE FLIES IN THE LABORATORY only under the following circumstances:

> If any undesirable side effect or reaction occurs following the administration of the test product(s), and if ICR has employed reasonable care in the development of the protocol and has not violated any local, state or federal laws pertaining to the administration of chemical substances, medical devices, drugs or biological agents, including but not limited to the Federal Insecticide, Fungicide, and Rodenticide Act, as amended, and the Federal Food, Drug and Cosmetic Act of 1938, as amended, and the regulations promulgated pursuant thereto, LANXESS shall indemnify and hold harmless ICR against any and all claims, lawsuits and judgements thereon (including reasonable attorney's fees through the appellate level) which may be brought against it as a result of the development or implementation of the protocol.
>
> In the event any such claim is made or lawsuit is initiated, ICR shall give prompt written notice thereof to LANXESS, shall permit LANXESS or its insurance carrier to defend such claim or lawsuit, and shall cooperate fully in any such defense.

ICR, Inc.
Accepted By:

Name: Robin G. Todd
Robin G. Todd, PhD, BCE

Title: Director

Date: 1/24/08

LANXESS Corporation
Accepted By:

Name: Raymond Newhouse
Raymond Newhouse

Title: Chief Financial Officer

Date: _____

# SITE APPLICATION LETTER



Date 1/23/2008

Chairman
Essex Institutional Review Board, Inc.
121 Main Street
Lebanon, NJ 08833-2162

In connection with the **[Sponsor]** LANXESS Corporation clinical research project, entitled:

**[Protocol Title] Evaluation of the Efficacy of KBR 3023 (Picaridin: Icaridin) - Based Personal Insect Repellents (20% Cream and 20% Spray) Against Stable Flies in the Laboratory**

and **[Protocol number]** G4330108001A382

application is being made to the Essex Institutional Review Board for review under the provisions of 21 CFR 50, 21 CFR 56, 45 CFR 46, and 40 CRF 26.

**The following information will assist the Essex IRB review of your request. All questions must be answered completely.**

**You must transmit this letter for each site requesting review and approval.**

**1.** ☐ A Form 1572 (if applicable to this study) listing each research site is attached.

☒ A Form 1572 is not applicable to this study. A copy of the Investigator Attestation Form is attached.

☐ A copy of a valid IND, when one is required. A copy of the Form 1572 or a copy of the Investigator Attestation Form is attached.

☐ For device study, attach IDE letter from the FDA or statement supporting non-significant risks or why exempt from IDE requirements under 21 CFR 812.2 or otherwise exempt. A copy of the Investigator Attestation Form is attached.

---

**2a. Research Site: (Complete a separate letter for each site seeking approval.)**

Name: ICR, Inc.

Address: 1330 Dillon Heights Avenue

Baltimore, MD 21228

Office
Phone: 410 747-4500 Fax: 410 747-4928

24 Hour
Emergency
Number: 410 207-0415

How many clinical research studies are currently underway at this site? None

---

**2b.** Does the site have an adequate facility and number of staff to conduct the research and protect the safety and welfare of subjects?

☒ **Yes**

☐ **No (Please explain)**

**2c.** A site should ensure that adequate medical care is provided to subjects for any adverse events. Does the site have a policy and provisions for handling adverse reactions, including abnormal lab results or psychological events related to the trial?

☒ **Yes**

☐ **No (Please explain)**

---

**3.** Can the principal investigator be reached 24-hours a day? (**NOTE**: Answering machines not acceptable)

☒ **Yes**

☐ **No (Please explain)**

---

**4.** **Hospital to be used in an emergency:** **Distance from site: 7 miles**

Name: St. Agnes Hospital

Address: 900 S. Caton Avenue

Baltimore, MD 21229

Phone: 410 368-2389

Is this hospital equipped to handle adverse reactions?

☒ **Yes**

☐ **No**

---

**5.** The research site listed in question 2a is [check all boxes that apply]:

**a)** ☐ Independent private practice(s).

**b)** ☐ Private practice(s) located within a hospital or teaching institution.

**c)** ☐ Hospital(s) or teaching institution(s) **without** a local IRB.

**d)** ☒ Other [specify]: contract testing laboratory

[if only 5a, 5b, 5c and/or 5d are selected, skip to question 7]

**e)** ☐ Hospital(s) or teaching institution(s) with a local IRB.

| | | | |
|---|---|---|---|
| **6.** | The local IRB could have jurisdiction over this study. | ☐ **Yes** *[if yes, attach local IRB waiver letter]* | ☒ **No** |

| | | | |
|---|---|---|---|
| **7.** | The local IRB has restrictions on independent IRB approval of this study for the listed site. | ☐ **Yes** *[if yes, attach listing of restrictions]* | ☒ **No** |
| **8.** | Has this protocol been submitted to, reviewed by, disapproved, terminated and/or withdrawn from another IRB? | ☐ **Yes** *[if yes, attach IRB findings]* | ☒ **No** |
| **9.** | Is there a local community attitude that could impact on the manner in which your study will be conducted? | ☐ **Yes** *[if yes, attach listing of attitudes]* | ☒ **No** |
| **10.** | Please provide the names of the sub-investigators in this study. **If none, please write "NONE".** (This includes any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial –related decisions.) (If necessary, please attach an addendum providing the names of the sub-investigators)<br><br>NOTE: These names must be listed on the 1572 form [Box 6], if required by this study type.<br><br>**Include resume(s) and current license(s)/certification.** | Charles Cornell<br><br>Timothy Foard<br><br>Niketas Spero<br><br>Gloria Stevens<br><br>Fouad Zgidou<br><br>CVs are on file at Essex IRB | |
| **11.** | Do you personally attend to research participants at this site?<br><br>If "**No**", list the names of those who attend the participants:<br><br>***Include resume(s) and current license(s)/certification.*** | ☒ **Yes** | ☐ **No** |

**12.** In your absence, research-related medical emergencies are handled by which healthcare giver?

First Aid trained personnel: Niketas Spero

***Include resume(s) and current license(s)/certification.***

13. a. How will you identify and recruit potential subjects? From a list of past study participants who are willing to participate in studies

b. Will there be any bonus payment for recruiting participants? ☐ **Yes** ☒ **No**

If yes, please explain and submit amounts

c. Will any payment to subjects be coercive or apply an undue influence to participate?

☐ **Yes (Please explain)**

☒ **No**

d. Are some or all of the participants likely to be vulnerable, (children, newborns, fetuses, pregnant, or lactating women, cognitively impaired, prisoners)?

☐ **Yes (Please explain and state any safeguards)**

☒ **No**

e. What provisions have you in place to protect the privacy and confidentiality of participants, including HIPAA compliance, during and after the study? **subjects names and any medical issues will be kept confidential**

14. Will subjects be eligible to participate in any additional studies during this trial?

☒ **Yes (Please explain)** ☐ **No**

Subjects may be able to participate in both the dose determination phase of the study and the repellent test phase of the study

15. Please provide information about the planned methods for obtaining informed consent.

I. When will the consent process take place? on the day of the study, prior to study commencement, or on a prior day

II. Where will the consent process take place? at ICR, Inc. in Baltimore, MD

III. How will you verify whether the subject understands or has the capacity to comprehend what has been explained the consent process?
we will ask them questions to verify their understanding, and then have them initial each page of the ICD, and sign at the end to signify their comprehension.

IV. Will you provide the opportunity for the prospective subjects to consider whether or not to participate? ☒ **Yes** ☐ **No (Please explain)**

V. For studies of greater than one year duration, will you be reviewing the consent form again with the subject? ☐**Yes** ☐ **No (Please explain)**
Each of the 2 phases of the study will last only 1 day



VI. What plan do you have to assure decisionally-impaired individuals will have the capacity

to give consent and participate? Our subjects will be able to freely give their informed consent after weighing the risks and benefits. If we do not feel that they are capable of making the consent decision by themselves, we will not accept them into the study.

**16.** Please list the individuals other than the principal investigator and sub-investigator(s) as requested below. If none, please write "NONE". **Include resume(s) and current license(s)/certification.**

**a.** Individual(s) who will administer the consent form at this site:

none

**b.** Individual(s) involved with this study (include responsibility):

Charles Cornell, Timothy Foard, Niketas Spero, GLoria Stevens and Fouad Zgidou - all will observe repellent dosing and record stable fly bites

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**17.** **a.** Will a non-English consent form be required for your study population? ☐ **Yes** ☒ **No (skip to Q. 18)**

**b.** If so, what language(s)?

Would you like Essex IRB to contract for this service? ☐ **Yes** ☐ **No**

If **"Yes"**, consult the Essex IRB Fee Schedule for estimated fees.
If **"No"**, consult the "submission guidelines" for translation certification required.

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**18.** Has the Food and Drug Administration (FDA), Office for Human Research Protections (OHRP), or other any regulatory agency, inspected this site and/or investigators? ☐ **Yes** (Continue with next question) ☒ **No (Skip to Q. 19)**

If inspected, include any related correspondence (example FDA Form 483/EIR report) for Board review.

Was a Warning Letter subsequently issued? ☐ **Yes** (If yes, attach copy(ies) of all correspondence for Board review) ☐ **No**

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**19.** Has the FDA, OHRP or any regulatory agency, a Sponsor, or an IRB ever terminated a study at this site? ☐ **Yes** (If yes, attach explanation for Board review) ☒ **No**

---

**20.** Does this site have established, written standard operating procedures? ☒ **Yes** ☐ **No**

---

| | | | |
|---|---|---|---|
| **21.** | **a.** Does this site have ongoing training for investigators and staff in clinical research procedures in addition to any professional licenses and/or certifications?<br><br>If yes, please provide a memo stating the type of training (i.e. ACRP, NIH, in-house training, seminars, literature, staff meetings, etc.). Provide any certificates, letters, etc. if applicable. | ☒ **Yes** | ☐ **No** |
| | **b.** Does anyone plan to become certified? | ☒ **Yes** | ☐ **No** |
| | **c.** May we assist anyone in obtaining certification? | ☐ **Yes** | ☒ **No** |

**22.** We need to know if you or anyone involved with this research has any financial or nonfinancial conflict of interest (COI) that could compromise or lessen the safety and welfare of subjects who enroll in the study. Please complete the separate Investigator Conflict of Interest Form and submit with this form.

**Please complete the separate Investigator Conflict of Interest Form and submit with this form.**

The threshold amount is $50,000 or greater for FDA related studies; $10,000 or greater for OHRP reglated studies or more equity in the sponsor. If you qualify for a COI, please attach a separate sheet to describe how it will be managed and who will have the authority to impose those measures, how subjects and others will be informed and whether you have a COI Committee or equivalent backed by policies and procedures.

**23. CERTIFICATION –**

**Your signature below certifies that:**

a) Selection of participants for the above research study will be on an equitable basis and that all participants will be treated fairly;

b) informed consent will be sought from each prospective participant or the participant's legally authorized representative;

c) the research site listed in question 2a is appropriately equipped to handle adverse reactions should they occur;

d) adverse reactions and unexpected (unanticipated) events events will be reported to the Sponsor (for notification to the FDA or other regulatory agencies and other investigators), with a copy forwarded to the IRB within 15 working days after the event;

e) where appropriate, the study will, by design and intent, undergo strict adherence to design and monitoring to ensure the saftey and welfare of the participants;

f) any FDA, OHRP, or any regulatory agency site audits leading to a Form 483 or Warning Letter will be promptly reported to Essex IRB for its review and determination of adequacy of responses and corrective actions;

**23. CERTIFICATION – continued**

g) any participant recruitment material (which includes but is not limited to printed media; video and audio tape) will be submitted to the IRB for review and approval prior to its release to the study population;

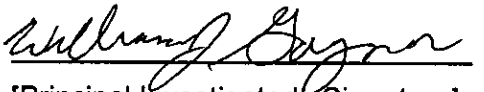
h) you shall provide a periodic, continuing review report prior to the expiration date of the approval and a final report no later than 90 days after completion of your participation in the study (last study participant contact); and,

i) you have examined this application letter and any accompanying documentation, and to the best of your knowledge and belief, they are true, correct, and complete.

**j) State laws shall be observed during the conduct of the study.**

**YOU WILL NOT COMMENCE ANY RESEARCH ACTIVITY (INCLUDING SCHEDULING) UNTIL YOU HAVE RECEIVED WRITTEN APPROVAL TO DO SO BY ESSEX IRB.**

**SIGNATURE:**



**1/23/2008**

[Principal Investigator's Signature] [Date]

William J. Gaynor BS, MS

[Printed Name and Degrees]

**DOCUMENT MAILING ADDRESS:**


ICR, Inc.

[office street address 1]

1330 Dillon Heights Ave

[office street address 2]

Baltimore, MD 21228

[city, state, ZIP code]

410 747-4500 [phone number]

410 747-4928 [fax number]

wgaynor@icrlab.com

e-mail address and name of Study Contact Person


Version: October 1, 2007

ICR | *Independent Laboratory*
*Pesticide Efficacy Testing*
*Regulatory Services*

January 23, 2008

Essex Institutional Review Board, Inc.
121 Main Street
Lebanon, NJ 08833-2162

Subject: Memo regarding ongoing training for investigators and staff in clinical research procedures

Dear Dr. Lambert:

ICR, Inc. Provides ongoing training for all investigators and staff for compliance with Good Laboratory Practices, comprehension of and adherence to internal GLPs, and any necessary continuing education. In addition to this training, one of our investigators is currently enrolled in a self-paced Web course entitled "RAN 9002 Informed Consent Process Training without CE Curriculum. I have completed this course. All of our other potential investigators will be encouraged to enroll in and complete the above online course.

Please do not hesitate to contact me with any questions.

Sincerely,

William J. Gaynor

William J. Gaynor
Study Director
ICR, Inc.

**ESSEX INSTITUTIONAL REVIEW BOARD, INC.**

## Investigator Attestation

**Qualifications:** I am qualified by education, training and experience to assume responsibility for the proper conduct of the following research study:

Sponsor Name: LANXESS Corporation

Protocol Name: Evaluation of the Efficacy of KBR 3023 (Picaridin: Icaridin) - Based Personal Insect Repellents (20% Cream and 20% Spray) Against Stable Flies in the Laboratory

Protocol Number: G4330108001A382

- Any patients and participants involved in the research shall be informed of the procedures related to the research study, ensuring that consent has been obtained in accordance with 21 CFR 50, as it relates to IRB review and approval.

- Essex IRB is in compliance with 21 CFR 50 and 56 and 45 CFR 46, and is responsible for the initial and continuing review of all changes, recruitment procedures, safety reporting and annual review of the research site(s). The investigator shall promptly report to the Essex IRB any changes in research activity and all unanticipated (adverse) events involving risks to human subjects or others.

- Changes to the research plan and/or participant consent form shall not be made without the approval of Essex IRB, with the exception of the elimination of apparent immediate hazards to human subjects.

- Past performance as an investigator where the Food & Drug Administration (FDA) and/or the Office of Human Research Protection (OHRP) inspection(s) or audit(s) led to recommendations for corrective actions, sanctions, or disqualification (FDA Form 483, FDA Warning Letter, etc.) will be submitted to the Essex IRB, along with documentation of resolution of the issue(s).

- Resources to conduct the research study in a manner providing protection to human participants in the study will be employed, including, but not limited to: adequate qualified staff and facilities; providing information and necessary training with regard to the protocol, the test product, and duties and functions. It is the obligation of the Principal Investigator to oversee all aspects of the study, providing adequate medical (or dental) care, as indicated.

- The Principal Investigator certifies compliance with 21 CFR 54 regulations regarding financial interest in the outcome of the research and to minimize bias in the design, conduct, reporting and analysis of the study. Disclosure of certain financial arrangement with the Sponsor will be made available to the Essex IRB upon request or at site inspection.

**Attestation:** I will comply with applicable regulatory requirements, ICH Guidelines and Good Clinical Practices. I understand my responsibilities as Principal Investigator in conducting research. I am familiar with human research protection regulations and will strictly adhere to these regulations.

William J. Gaynor — Printed Name of Principal Investigator

William J. Gaynor — Signature of Principal Investigator

1/23/2008 — Date

# ESSEX IRB

## INVESTIGATOR CONFLICT OF INTEREST DECLARATION

Study title and number: "Evaluation of the Efficacy of KBR 3023 (Picaridin: Icaridin) - Based Personal Insect Repellents (20% Cream and 20% Spray) Against Stable Flies in the Laboratory". ICR Project Number: 0108-433-0161

Sponsor: LANXESS Corporation

Financial relationships of investigators (or institutions/sites) to sponsors have the potential to adversely affect the rights and welfare of human subjects involved in research. In order to help ensure that such issues do not compromise the results or create hazards for the subjects, Essex IRB requests you to make a declaration regarding any conflict of interest (COI) in the conduct or outcome of the trial. To achieve this, we ask you to answer the following questions and submit a response to any that have a "Yes" reply in a separate letter.

- Do you have any relationship with the sponsor or institution that could cause potential or actual conflict of interest? Yes ☐ No ☒
  If yes, describe the degree of conflict and with which parties.
- Is there any compensation that your institutional ethics/COI committee has deemed to be a conflict or could affect the outcome of the trial?
  Yes ☐ No ☒ If yes, describe.
- Does anyone involved with the research have proprietary interests in the product, drug or device, including patents, trademarks, copyright and licensing agreements? Yes ☐ No ☒ If yes, describe.
- Does anyone have an equity interest in the research sponsor?
  Yes ☐ No ☒ Describe, if yes.
- Do you receive significant payments, equipment, retainers, incentives, grants or honoraria from the sponsor? Yes ☐ No ☒ If yes, describe.
- Are the payments or incentives you receive per participant considered to be outside the norm? Yes ☐ No ☒ If yes, describe.

You may submit a letter from your institution's COI Committee regarding their determination of any COI in this study. Any recommendations you or they make to reduce or eliminate any COI will be appreciated. Examples of these are: describing any COI in the informed consent form, having an impartial third party obtain consent, reduction or elimination of the financial interest or equity ($50000 or greater), monitoring by an impartial party (independent data and safety committee), or separation of duties or roles (e.g., change of principal investigator). Violation of this declaration may result in it being reported to the FDA or OHRP (Office for Human Research Protection), as well as, our terminating approval for you to conduct this research study.

We thank you for indulgence in completing this document. If you have any questions, please contact us.

Principal Investigator's Printed Name: William J. Gaynor

Signature: William J Gaynor Date: 1/23/2008

**EIRB RESPONSE TO ORIGINAL ICR SUBMISSION**

**Essex Institutional Review Board, Inc.**
121 Main Street • Lebanon, New Jersey 08833
Telephone (908) 236-7735 • Fax (908) 236-2027
www.essexirb.com

January 30, 2008

William J. Gaynor
Insect Control & Research, Inc.
1330 Dillon Heights Avenue
Baltimore, MD 21228

Dear Mr. Gaynor:

On January 28, 2008 the Essex Institutional Review Board met and reviewed the LANXESS Corporation clinical research project, "Evaluation of the Efficacy of KBR 3023 (Picaridin; Icaridin)-Based Personal Insect Repellents (20% Cream and 20% Spray) Against Stable Flies in the Laboratory" (G4330108001A382, 1/21/08).

The **Protocol** (dated 1/21/08) reviewed by a full board, was conditionally approved pending the following non-substantive modifications recommended by the board:

**Page 3:**

- Under **Table of Contents**, section **22. Data Analysis, item b, Methodology** – Please replace the page number "26" with the number "27" to match the content of the protocol.

**Page 15:**

- Under section j. Recruitment Procedures, 2nd paragraph – Please submit the "telephone script" as a stand-alone document. As a stand-alone document, the document must have its own page numbers (i.e. Page 1 of 1), protocol number and version date and some Subject No. line (or however you will identify the subject). The telephone script may stay in the protocol, but a second stand-alone document must be submitted for review.

**Page 18:**

- Under section **13. RATIONALE FOR NOT HAVING POSITVE CONTROLS,** line 6 - Please add a period after the words "would be ethical".

**Page 19:**

- Under section **RISK CHARACTERIZATION AND MINIMIZATION** – Please give this section the number "**17.**" to coincide with the Table of Contents.

**Page 20:**

- Under 1st paragraph, top of page, line 13 – Please replace the words "study **will** substantially exceed" with the words "study **will not** substantially exceed".

- Continued on Next Page -

**Page 21:**

- Under section *Arthropod-borne diseases,* 2nd paragraph, line 2 –Please replace the words "**will not** exposed" with the words "**will not be** exposed".
- Section title **19. DISCOMFORT AND HAZARD (EIRB Mandated Section)** - Please replace the section the number "**19**." with the number "**18**" to coincide with the Table of Contents. Also, please verify that the words "(EIRB Mandated Section)" should be "(EPA Mandated Section)". If it is not "EPA", then please delete the words "EIRB Mandated Section".
- Under section **19. DISCOMFORT AND HAZARD,** 2nd paragraph, line 3 – Please add a period and a space after the words "for payment".
- Under section **19. DISCOMFORT AND HAZARD,** 2nd paragraph, line 5 – Please replace the word "**enquire**" with the word "**inquire**".
- Section title **20. BENEFITS** - Please replace the section the number "**20.**" with the number "**19"** to coincide with the Table of Contents.

**Page 22:**

- Section title **21. REPELLENT TEST METHODS** - Please replace the section the number "**21.**" with the number "**20"** to coincide with the Table of Contents.
- Under section **21. REPELLENT TEST METHODS, item a Experimental Design,** 2nd paragraph, line 4 – Please replace the words "either **till** two" with the words "either **until** two".

**Page 26:**

- Under section **v.**, line 1 – Please replace the word "**bites**" with the word "**bite**" (delete the letter "s").
- Section title **22. CONFIDENTIALITY** - Please replace the section the number "**22.**" with the number "**21"** to coincide with the Table of Contents.
- Section title **23. DATA ANALYSIS** - Please replace the section the number "**23.**" with the number "**22"** to coincide with the Table of Contents.

**Page 27:**

- Under section **b. Methodology**, 1st paragraph, line 4 - Please replace the words "either **till** two" with the words "either **until** two".
- Under section **c. Statistical Procedures, *Power***, line 4 – Please complete the sentence beginning with the words "Using information from their)".

**NOTE: When making the revisions to the Protocol, please remember to update the version date before re-submitting.**

- Continued on Next Page -

The **Consent Form – Dose Determination** (dated 1/21/08) reviewed by a full board, was conditionally approved pending the following non-substantive modifications recommended by the board:

**Page 2:**

- Under 1st paragraph, top of page, line 1 – Please replace the words "listed **on the next page**" with the words "listed **below**".
- Under 1st paragraph, top of page, line 3 – Please replace the words "Your **singing**" with the words "Your **signing**".
- Under 2nd paragraph, line 2 – Please delete the words "someone on" after the words "presence of".
- Under section **Eligibility for the Study**, bullet 1 – Please replace the words "**No exclusions**" with the words "**Six of each: Male and Female**".
- Under section **Eligibility for the Study**, bullet 5 – Please reformat so the bullet lines up with the other bullets in this section.
- Under section **Eligibility for the Study**, bullet 7 – Please replace the words "to **insect repellents**" with the words "to **insect bites/stings, repellents**".

**Page 3:**

- Under bullet 1, top of page – Please reformat the bullet to be the same size as the 2nd bullet. Also, decrease the indent of the sentence to match bullet 2.
- Under section **Dose Determination Phase Summary,** line 8 – Please delete the word "**ambient**" after the words "**at comfortable**".
- Under section **Procedures,** 1st sentence – Please reformat so this sentence is in the same style font and size as the rest of the consent form.
- Under section **Procedures,** bullet 2 – Please add the symbol "®" after the word "Neutrogena".

**Page 4:**

- Under section **Laboratory Study Details**, items 1 & 4 through 7 – Please correct formatting so that all sentences after the first sentence are left justified similar to items 2 & 3.
- Under section **Laboratory Study Details**, item 1 – After the words "repellent products." please add the sentence "**You must not observe or discuss with other subjects any of these procedures**."

**Page 5:**

- Items 8 through 13 - Please reformat so that all sentences are left justified.
- Section title **Discomfort and Hazard** – Please reformat to move this title to the next page so it is not a stand-alone title. After moving the title, add a "Blank Box" with the words "This space intentionally left blank" in the center of the box to the empty space left at the bottom of page 5. There can be only 1" or less of space between the last line of the last paragraph on a page and the footer.

klr

**Page 6:**

- 1st sentence, top of page – Please delete the sentence beginning with the words "You will be exposed to".
- Section title **Reaction to the test repellents** – Please add a colon after the word "repellent" Also, please correct formatting so that the section title and the first and second paragraph are left justified to match the rest of the consent form.
- Under section **Reaction to the test repellents,** 2nd paragraph, line 2 – Please delete the word "acute" after the words "demonstrated low".
- Under section **Reaction to the test repellents,** 2nd paragraph, line 4 – Please delete the word "acute" after the words "low toxicity".
- Under section **Reaction to the test repellents,** 2nd paragraph, line 10 – Please give examples/types of reaction to the test repellent.
- Under section **Reaction to the test repellents,** 3rd paragraph – Please delete the paragraph beginning with the words "The temperature and humidity".
- Under section **Reaction to the test repellents,** 4th paragraph, line 1 – Please delete the comma after the words "staff members".
- Under section **Reaction to the test repellents,** 4th paragraph, line 2 – Please delete the words "First-Aid-" after the word "and".
- Section title **Financial Consideration** - Please reformat to move this title to the next page so it is not a stand-alone title. After moving the title, add a "Blank Box" with the words "This space intentionally left blank" in the center of the box to the empty space left at the bottom of page 6. There can be only 1" or less of space between the last line of the last paragraph on a page and the footer.

**Page 7:**

- Under 1st paragraph, top of page, line 1 – Please add a period after the words "payment of $99".
- Under 1st paragraph, top of page, line 2 – Please delete the words "paid to you." at the beginning of this line.
- Under section **Benefits**, 1st paragraph, line 3 – Please delete the sentence beginning with the words "The sponsor, LANXESS Corporation will gain".
- Under section **Benefits**, 2nd paragraph, line 1 – Please replace the words "**is also likely to**" with the words "**may**".
- Under section **Benefits**, 2nd paragraph, line 2 – Please replace the words "**a potentially important public health pest.**" with the words "**a noxious pest.**"

**Page 8:**

- Under section **Alternative** – Please rewrite this sentence as follows: "**The only alternative is not to participate.**"
- After section **Alternative** - Please add a new section titled "**NEW INFORMATION**" and add the following paragraph: "You will be informed verbally or in writing of any significant new findings discovered during the course of this study which may influence your continued participation."

klr

**Page 8 (continued):**

- After the new section **New Information** – Please add a new section titled **Voluntary Participation/Withdrawal** and add the following new paragraph: "You may be withdrawn from the study even if you want to continue. This could happen if (1) the study doctor believes it is in your best interest for you to stop being in the study, (2) or if you do not follow instructions for the study, (3) or if the sponsor stops the study for administrative or any other reasons."
- Under section **Questions**, line 3 – Please replace the words "**or related concerns**," with the words "**or any related concerns or complaints,**".
- After section **Questions** - Please add a new section titled "**Research Participation Information**" and the following paragraph:

  "You can obtain information about participating in research studies from a number of sources.
  A few are:
  - Center for Information and Study on Clinical Research Participation (CISCRP): www.ciscrp.org
  - Food and Drug Administration (FDA): www.fda.gov
  - Office for Human Research Protections (OHRP): www.hhs.gov/ohrp
  - National Institute of Health: clinical trials.gov
  - National Cancer Institute: www.nci.nih.gov
  - CenterWatch: www.centerwatch.com
  - Various large university websites
  - Various associations and societies concerned with specific diseases websites."

- Section title **Consent** - Please reformat to move this title to the next page so it is not a stand-alone title.

**Page 9:**

- Under **Signature** lines – Please add a "**Printed Name of Subject**" line before the Subject's Signature line. Also, please replace the words "Signature of Witness" with the words "Signature of Person Obtaining Consent". Then reformat to move the "Signature of Person Obtaining Consent" and "Date" line to its own line below the Subject's Signature line.

**NOTE: When making the revisions to the Consent Form – Dose Determination, please remember to update the version date before re-submitting.**

The **Consent Form – Repellent Test** (dated 1/21/08) reviewed by a full board, was conditionally approved pending the following non-substantive modifications recommended by the board:

**Page 2:**

- Under 1st paragraph, line 2 - Please delete the words "someone on" after the words "presence of".

**Page 2 (continued):**

- Under section **Eligibility for the Study**, bullet 1 – Please replace the words "**No exclusions**" with the words "**Six of each: Male and Female (plus one extra of either sex)**".
- Under section **Eligibility for the Study**, bullets 5 & 6 – Please reformat so the bullet lines up with the other bullets in this section.
- Under section **Eligibility for the Study**, bullets 5 through 6 – Please reformat so that the sentences of these paragraphs are all left justified.
- Under section **Eligibility for the Study**, bullet 8, line 2 – Please add a period after the words "skin care products".
- Under section **Eligibility for the Study**, bullet 9 - Please reformat so that this sentence is left justified.
- Under section **Eligibility for the Study**, bullet 10 – Please reformat so that this bullet and sentence line up with the other bullets and sentences (once they are reformatted).

**Page 3:**

- Under 1st sentence, top of page - Please reformat so that the sentence is left justified.
- Under 1st bullet, top of page, line 1 - Please reformat so that the sentence is left justified.
- Under section **Laboratory Repellent Phase Summary**, 1st paragraph, line 2 – Please replace the words "**selected by lot**" with the words "**selected by chance (like pulling a number out of a hat)".**
- Under section **Laboratory Repellent Phase Summary**, 1st paragraph, line 5 - Please delete the word "**ambient**" after the words "**at comfortable**".
- Under section **Laboratory Repellent Phase Summary**, 1st paragraph, line
- Under section **Procedures,** 1st sentence – Please reformat so this sentence is in the same style font and size as the rest of the consent form.

**Page 4:**

- 1st bullet, top of page - Please add the symbol "®" after the word "Neutrogena".
- Under section **Laboratory Study Details**, item 1 - Please replace the words "**selected by lot**" with the words "**selected by chance (like pulling a number out of a hat)".**
- Under section **Laboratory Study Details**, item 4 - Please reformat so that all sentences are left justified to match the paragraphs of items 1-3.

**Page 5:**

- 1st sentence, top of page & items 5 through 10 - Please reformat so that all sentences are left justified.
- Under item 10, line 8 – Please add a comma after the word "Nonetheless".

**Page 6:**

- Under items 11 through 13 - Please reformat so that all sentences are left justified.
- Under item 13, line 2 – Please replace the number "**20**" with the word "**twenty**".
- Under section **Discomfort and Hazard** - Please delete the sentence beginning with the words "You will be exposed to".

klr

**Page 7:**

- Under section **Reaction to the test repellents**, 2nd paragraph, line 2 – Please delete the word "acute" after the words "demonstrated low".
- Under section **Reaction to the test repellents**, 2nd paragraph, line 4 - Please delete the word "acute" after the words "low toxicity".

**Page 8:**

- 1st paragraph, top of page – Please reformat so that this entire paragraph is left justified.
- 1st paragraph, top of page, line 6 - Please give examples/types of reaction to the test repellent.
- 3rd paragraph, top of page - Please delete the paragraph beginning with the words "The temperature and humidity".
- 4th paragraph, line 1 - Please delete the comma after the words "staff members".
- 4th paragraph, line 2 - Please delete the words "First-Aid-" after the word "and".
- Under section **Financial Consideration**, line 3 – Please add a period after the words "payment of $134" and then delete the words "paid to you."

**Page 9:**

- Under section **Benefits**, 1st paragraph, line 1 – Please delete the sentence beginning with the words "The sponsor, LANXESS Corporation will gain".
- Under section **Benefits**, 2nd paragraph, line 1 – Please replace the words "**is also likely to**" with the words "**may**".
- Under section **Benefits**, 2nd paragraph, line 1 – Please delete the sentence beginning with the words "The sponsor, LANXESS Corporation will gain".
- Under section **Benefits**, 2nd paragraph, line 2 – Please replace the words "**a potentially important public health pest.**" with the words "**a noxious pest.**"
- Under section **Alternative** – Please rewrite this sentence as follows: "**The only alternative is not to participate.**"
- After section **Alternative** - Please add a new section titled "**New Information**" and add the following paragraph: "You will be informed verbally or in writing of any significant new findings discovered during the course of this study which may influence your continued participation."
- After the new section **New Information** – Please add a new section titled **Voluntary Participation/Withdrawal** and add the following new paragraph: "You may be withdrawn from the study even if you want to continue. This could happen if (1) the study doctor believes it is in your best interest for you to stop being in the study, (2) or if you do not follow instructions for the study, (3) or if the sponsor stops the study for administrative or any other reasons."
- Under section **Questions**, line 3 – Please replace the words "**or related concerns**," with the words "**or any related concerns or complaints**,".

- Continued on Next Page -

**Page 9 (continued):**

- After section **Questions** - Please add a new section titled **"Research Participation Information"** and the following paragraph:

  "You can obtain information about participating in research studies from a number of sources.
  A few are:
  - Center for Information and Study on Clinical Research Participation (CISCRP): www.ciscrp.org
  - Food and Drug Administration (FDA): www.fda.gov
  - Office for Human Research Protections (OHRP): www.hhs.gov/ohrp
  - National Institute of Health: clinical trials.gov
  - National Cancer Institute: www.nci.nih.gov
  - CenterWatch: www.centerwatch.com
  - Various large university websites
  - Various associations and societies concerned with specific diseases websites."

**Page 10:**

- Under **Signature** lines – Please add a **"Printed Name of Subject"** line before the Subject's Signature line. Also, please replace the words "Signature of Witness" with the words "Signature of Person Obtaining Consent". Then reformat to move the "Signature of Person Obtaining Consent" and "Date" line to its own line below the Subject's Signature line.

**NOTE: When making the revisions to the Consent Form – Repellent Test, please remember to update the version date before re-submitting.**

Motion was called by Glenn Lambert to **conditionally approve** the study. There being no further discussion the roll was called. Motion carried. All meeting votes were unanimous with a vote of 5:0 with a sustained quorum. There were no controverted issues and there was no conflict of interest for any of the Board members in attendance. Approvals will be for one year from date of site notification.

**Please be reminded that the study may not commence any research activity (including scheduling) until formal, written approval and a stamped consent form is received by the research site.**

We look forward to receiving your revised consent form and responses to the questions raised by the Board. Thank you for the opportunity to work with you on this project.

Sincerely,

Glenn P. Lambert

Glenn Lambert, MD
Chairman

klr

# Meeting Minutes

## LANXESS Corporation
## G4330108001A382

On **January 28, 2008** the Essex Institutional Review Board met and reviewed the LANXESS Corporation clinical research project, "Evaluation of the Efficacy of KBR 3023 (Picaridin; Icaridin)- Based Personal Insect Repellents (20% Cream and 20% Spray) Against Stable Flies in the Laboratory" (G4330108001A382, 1/21/08).

On **January 28, 2008**, the Board met at 121 Main Street, Lebanon, NJ 08833 at 4:00 p.m. Board members present: **Glenn P. Lambert, MD** (Chairman), **Loretta P. Szczepanski, RN** and **Deborah A. Timmerman**. Alternate Board Members: **Louise M. Doughtery, RN** (Alternate for Thomas G. McElrath, MD), and **James L. Harris** (Alternate for Philip B. Carr-Jones, M Div). The following individuals were also present to take minutes: Karen Radcliffe Glenn P. Lambert, MD, FAAP chaired the meeting.

**Glenn P. Lambert, MD** called the meeting to order at 4:00 p.m.

The **Protocol** (dated 1/21/08) reviewed by a full board, was conditionally approved pending the following non-substantive modifications recommended by the board:

**Page 3:**

- Under **Table of Contents**, section **22. Data Analysis, item b, Methodology** – Please replace the page number "26" with the number "27" to match the content of the protocol.

**Page 15:**

- Under section j. Recruitment Procedures, 2nd paragraph – Please submit the "telephone script" as a stand-alone document. As a stand-alone document, the document must have its own page numbers (i.e. Page 1 of 1), protocol number and version date and some Subject No. line (or however you will identify the subject). The telephone script may stay in the protocol, but a second stand-alone document must be submitted for review.

**Page 18:**

- Under section **13. RATIONALE FOR NOT HAVING POSITVE CONTROLS,** line 6 - Please add a period after the words "would be ethical".

**Page 19:**

- Under section **RISK CHARACTERIZATION AND MINIMIZATION** – Please give this section the number "**17.**" to coincide with the Table of Contents.

**Page 20:**

- Under 1st paragraph, top of page, line 13 – Please replace the words "study **will** substantially exceed" with the words "study **will not** substantially exceed".

- Continued on Next Page -

**Page 21:**

- Under section *Arthropod-borne diseases,* 2nd paragraph, line 2 –Please replace the words "**will not** exposed" with the words "**will not be** exposed".
- Section title **19. DISCOMFORT AND HAZARD (EIRB Mandated Section)** - Please replace the section the number "**19.**" with the number "**18**" to coincide with the Table of Contents. Also, please verify that the words "(EIRB Mandated Section)" should be "(EPA Mandated Section)". If it is not "EPA", then please delete the words "EIRB Mandated Section".
- Under section **19. DISCOMFORT AND HAZARD,** 2nd paragraph, line 3 – Please add a period and a space after the words "for payment".
- Under section **19. DISCOMFORT AND HAZARD,** 2nd paragraph, line 5 – Please replace the word "**enquire**" with the word "**inquire**".
- Section title **20. BENEFITS** - Please replace the section the number "**20.**" with the number "**19**" to coincide with the Table of Contents.

**Page 22:**

- Section title **21. REPELLENT TEST METHODS** - Please replace the section the number "**21.**" with the number "**20**" to coincide with the Table of Contents.
- Under section **21. REPELLENT TEST METHODS, item a Experimental Design,** 2nd paragraph, line 4 – Please replace the words "either **till** two" with the words "either **until** two".

**Page 26:**

- Under section **v.**, line 1 – Please replace the word "**bites**" with the word "**bite**" (delete the letter "s").
- Section title **22. CONFIDENTIALITY** - Please replace the section the number "**22.**" with the number "**21**" to coincide with the Table of Contents.
- Section title **23. DATA ANALYSIS** - Please replace the section the number "**23.**" with the number "**22**" to coincide with the Table of Contents.

**Page 27:**

- Under section **b. Methodology**, 1st paragraph, line 4 - Please replace the words "either **till** two" with the words "either **until** two".
- Under section **c. Statistical Procedures, *Power***, line 4 – Please complete the sentence beginning with the words "Using information from their)".

**NOTE: When making the revisions to the Protocol, please remember to update the version date before re-submitting.**

- Continued on Next Page -

The **Consent Form – Dose Determination** (dated 1/21/08) reviewed by a full board, was conditionally approved pending the following non-substantive modifications recommended by the board:

**Page 2:**

- Under 1st paragraph, top of page, line 1 – Please replace the words "listed **on the next page**" with the words "listed **below**".
- Under 1st paragraph, top of page, line 3 – Please replace the words "Your **singing**" with the words "Your **signing**".
- Under 2nd paragraph, line 2 – Please delete the words "someone on" after the words "presence of".
- Under section **Eligibility for the Study**, bullet 1 – Please replace the words "**No exclusions**" with the words "**Six of each: Male and Female**".
- Under section **Eligibility for the Study**, bullet 5 – Please reformat so the bullet lines up with the other bullets in this section.
- Under section **Eligibility for the Study**, bullet 7 – Please replace the words "to **insect repellents**" with the words "to **insect bites/stings, repellents**".

**Page 3:**

- Under bullet 1, top of page – Please reformat the bullet to be the same size as the 2nd bullet. Also, decrease the indent of the sentence to match bullet 2.
- Under section **Dose Determination Phase Summary,** line 8 – Please delete the word "**ambient**" after the words "**at comfortable**".
- Under section **Procedures,** 1st sentence – Please reformat so this sentence is in the same style font and size as the rest of the consent form.
- Under section **Procedures,** bullet 2 – Please add the symbol "®" after the word "Neutrogena".

**Page 4:**

- Under section **Laboratory Study Details**, items 1 & 4 through 7 – Please correct formatting so that all sentences after the first sentence are left justified similar to items 2 & 3.
- Under section **Laboratory Study Details**, item 1 – After the words "repellent products." please add the sentence "**You must not observe or discuss with other subjects any of these procedures**."

**Page 5:**

- Items 8 through 13 - Please reformat so that all sentences are left justified.
- Section title **Discomfort and Hazard** – Please reformat to move this title to the next page so it is not a stand-alone title. After moving the title, add a "Blank Box" with the words "This space intentionally left blank" in the center of the box to the empty space left at the bottom of page 5. There can be only 1" or less of space between the last line of the last paragraph on a page and the footer.

**Page 6:**

- 1st sentence, top of page – Please delete the sentence beginning with the words "You will be exposed to".
- Section title **Reaction to the test repellents** – Please add a colon after the word "repellent" Also, please correct formatting so that the section title and the first and second paragraph are left justified to match the rest of the consent form.
- Under section **Reaction to the test repellents,** 2nd paragraph, line 2 – Please delete the word "acute" after the words "demonstrated low".
- Under section **Reaction to the test repellents,** 2nd paragraph, line 4 – Please delete the word "acute" after the words "low toxicity".
- Under section **Reaction to the test repellents,** 2nd paragraph, line 10 – Please give examples/types of reaction to the test repellent.
- Under section **Reaction to the test repellents,** 3rd paragraph – Please delete the paragraph beginning with the words "The temperature and humidity".
- Under section **Reaction to the test repellents,** 4th paragraph, line 1 – Please delete the comma after the words "staff members".
- Under section **Reaction to the test repellents,** 4th paragraph, line 2 – Please delete the words "First-Aid-" after the word "and".
- Section title **Financial Consideration** - Please reformat to move this title to the next page so it is not a stand-alone title. After moving the title, add a "Blank Box" with the words "This space intentionally left blank" in the center of the box to the empty space left at the bottom of page 6. There can be only 1" or less of space between the last line of the last paragraph on a page and the footer.

**Page 7:**

- Under 1st paragraph, top of page, line 1 – Please add a period after the words "payment of $99".
- Under 1st paragraph, top of page, line 2 – Please delete the words "paid to you." at the beginning of this line.
- Under section **Benefits**, 1st paragraph, line 3 – Please delete the sentence beginning with the words "The sponsor, LANXESS Corporation will gain".
- Under section **Benefits**, 2nd paragraph, line 1 – Please replace the words "**is also likely to**" with the words "**may**".
- Under section **Benefits**, 2nd paragraph, line 2 – Please replace the words "**a potentially important public health pest.**" with the words "**a noxious pest.**"

**Page 8:**

- Under section **Alternative** – Please rewrite this sentence as follows: "**The only alternative is not to participate.**"
- After section **Alternative** - Please add a new section titled "**NEW INFORMATION**" and add the following paragraph: "You will be informed verbally or in writing of any significant new findings discovered during the course of this study which may influence your continued participation."

**Page 8 (continued):**

- After the new section **New Information** – Please add a new section titled **Voluntary Participation/Withdrawal** and add the following new paragraph: "You may be withdrawn from the study even if you want to continue. This could happen if (1) the study doctor believes it is in your best interest for you to stop being in the study, (2) or if you do not follow instructions for the study, (3) or if the sponsor stops the study for administrative or any other reasons."
- Under section **Questions**, line 3 – Please replace the words "**or related concerns**," with the words "**or any related concerns or complaints,**".
- After section **Questions** - Please add a new section titled **"Research Participation Information"** and the following paragraph:

  "You can obtain information about participating in research studies from a number of sources. A few are:
  - Center for Information and Study on Clinical Research Participation (CISCRP): www.ciscrp.org
  - Food and Drug Administration (FDA): www.fda.gov
  - Office for Human Research Protections (OHRP): www.hhs.gov/ohrp
  - National Institute of Health: clinical trials.gov
  - National Cancer Institute: www.nci.nih.gov
  - CenterWatch: www.centerwatch.com
  - Various large university websites
  - Various associations and societies concerned with specific diseases websites."

- Section title **Consent** - Please reformat to move this title to the next page so it is not a stand-alone title.

**Page 9:**

- Under **Signature** lines – Please add a "**Printed Name of Subject**" line before the Subject's Signature line. Also, please replace the words "Signature of Witness" with the words "Signature of Person Obtaining Consent". Then reformat to move the "Signature of Person Obtaining Consent" and "Date" line to its own line below the Subject's Signature line.

**NOTE: When making the revisions to the Consent Form – Dose Determination, please remember to update the version date before re-submitting.**

The **Consent Form – Repellent Test** (dated 1/21/08) reviewed by a full board, was conditionally approved pending the following non-substantive modifications recommended by the board:

**Page 2:**

- Under 1st paragraph, line 2 - Please delete the words "someone on" after the words "presence of".

- Continued on Next Page -

**Page 2 (continued):**

- Under section **Eligibility for the Study**, bullet 1 – Please replace the words "**No exclusions**" with the words "**Six of each: Male and Female (plus one extra of either sex)**".
- Under section **Eligibility for the Study**, bullets 5 & 6 – Please reformat so the bullet lines up with the other bullets in this section.
- Under section **Eligibility for the Study**, bullets 5 through 6 – Please reformat so that the sentences of these paragraphs are all left justified.
- Under section **Eligibility for the Study**, bullet 8, line 2 – Please add a period after the words "skin care products".
- Under section **Eligibility for the Study**, bullet 9 - Please reformat so that this sentence is left justified.
- Under section **Eligibility for the Study**, bullet 10 – Please reformat so that this bullet and sentence line up with the other bullets and sentences (once they are reformatted).

**Page 3:**

- Under 1st sentence, top of page - Please reformat so that the sentence is left justified.
- Under 1st bullet, top of page, line 1 - Please reformat so that the sentence is left justified.
- Under section **Laboratory Repellent Phase Summary**, 1st paragraph, line 2 – Please replace the words "**selected by lot**" with the words "**selected by chance (like pulling a number out of a hat)".**
- Under section **Laboratory Repellent Phase Summary**, 1st paragraph, line 5 - Please delete the word "**ambient**" after the words "**at comfortable**".
- Under section **Laboratory Repellent Phase Summary**, 1st paragraph, line
- Under section **Procedures,** 1st sentence – Please reformat so this sentence is in the same style font and size as the rest of the consent form.

**Page 4:**

- 1st bullet, top of page - Please add the symbol "®" after the word "Neutrogena".
- Under section **Laboratory Study Details**, item 1 - Please replace the words "**selected by lot**" with the words "**selected by chance (like pulling a number out of a hat)".**
- Under section **Laboratory Study Details**, item 4 - Please reformat so that all sentences are left justified to match the paragraphs of items 1-3.

**Page 5:**

- 1st sentence, top of page & items 5 through 10 - Please reformat so that all sentences are left justified.
- Under item 10, line 8 – Please add a comma after the word "Nonetheless".

**Page 6:**

- Under items 11 through 13 - Please reformat so that all sentences are left justified.
- Under item 13, line 2 – Please replace the number "**20**" with the word "**twenty**".
- Under section **Discomfort and Hazard** - Please delete the sentence beginning with the words "You will be exposed to".

**Page 7:**

- Under section **Reaction to the test repellents**, 2nd paragraph, line 2 – Please delete the word "acute" after the words "demonstrated low".
- Under section **Reaction to the test repellents**, 2nd paragraph, line 4 - Please delete the word "acute" after the words "low toxicity".

**Page 8:**

- 1st paragraph, top of page – Please reformat so that this entire paragraph is left justified.
- 1st paragraph, top of page, line 6 - Please give examples/types of reaction to the test repellent.
- 3rd paragraph, top of page - Please delete the paragraph beginning with the words "The temperature and humidity".
- 4th paragraph, line 1 - Please delete the comma after the words "staff members".
- 4th paragraph, line 2 - Please delete the words "First-Aid-" after the word "and".
- Under section **Financial Consideration**, line 3 – Please add a period after the words "payment of $134" and then delete the words "paid to you."

**Page 9:**

- Under section **Benefits**, 1st paragraph, line 1 – Please delete the sentence beginning with the words "The sponsor, LANXESS Corporation will gain".
- Under section **Benefits**, 2nd paragraph, line 1 – Please replace the words "**is also likely to**" with the words "**may**".
- Under section **Benefits**, 2nd paragraph, line 1 – Please delete the sentence beginning with the words "The sponsor, LANXESS Corporation will gain".
- Under section **Benefits**, 2nd paragraph, line 2 – Please replace the words "**a potentially important public health pest.**" with the words "**a noxious pest.**"
- Under section **Alternative** – Please rewrite this sentence as follows: "**The only alternative is not to participate.**"
- After section **Alternative** - Please add a new section titled "**New Information**" and add the following paragraph: "You will be informed verbally or in writing of any significant new findings discovered during the course of this study which may influence your continued participation."
- After the new section **New Information** – Please add a new section titled **Voluntary Participation/Withdrawal** and add the following new paragraph: "You may be withdrawn from the study even if you want to continue. This could happen if (1) the study doctor believes it is in your best interest for you to stop being in the study, (2) or if you do not follow instructions for the study, (3) or if the sponsor stops the study for administrative or any other reasons."
- Under section **Questions**, line 3 – Please replace the words "**or related concerns**," with the words "**or any related concerns or complaints**,".

- Continued on Next Page -

**Page 9 (continued):**

- After section **Questions** - Please add a new section titled "**Research Participation Information**" and the following paragraph:

  "You can obtain information about participating in research studies from a number of sources. A few are:
  - Center for Information and Study on Clinical Research Participation (CISCRP): www.ciscrp.org
  - Food and Drug Administration (FDA): www.fda.gov
  - Office for Human Research Protections (OHRP): www.hhs.gov/ohrp
  - National Institute of Health: clinical trials.gov
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  - CenterWatch: www.centerwatch.com
  - Various large university websites
  - Various associations and societies concerned with specific diseases websites."

**Page 10:**

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**NOTE: When making the revisions to the Consent Form – Repellent Test, please remember to update the version date before re-submitting.**

Motion was called by Glenn Lambert to **conditionally approve** the study. There being no further discussion the roll was called. Motion carried. All meeting votes were unanimous with a vote of 5:0 with a sustained quorum. There were no controverted issues and there was no conflict of interest for any of the Board members in attendance. Approvals will be for one year from date of site notification.

**Please be reminded that the study may not commence any research activity (including scheduling) until formal, written approval and a stamped consent form is received by the research site.**

Glenn P. Lambert, MD, FAAP
Chairman

1-30-08
1-30-08

**Essex Institutional Review Board, Inc.**
121 Main Street • Lebanon, New Jersey 08833
Telephone (908) 236-7735 • Fax (908) 236-2027
www.essexirb.com

January 30, 2008

On **January 28, 2008**, the Board met at 121 Main Street, Lebanon, NJ 08833 at 4:00 p.m. Board members present: **Glenn P. Lambert, MD** (Chairman), **Loretta P. Szczepanski, RN** and **Deborah A. Timmerman**. Alternate Board Members: **Louise M. Doughtery, RN** (Alternate for Thomas G. McElrath, MD), and **James L. Harris** (Alternate for Philip B. Carr-Jones, M Div). The following individuals were also present to take minutes: Karen Radcliffe Glenn P. Lambert, MD, FAAP chaired the meeting.

**Glenn P. Lambert, MD** called the meeting to order at 4:00 p.m.

**Old Business**
Investigator 483 Reports received during the previous week were made available for Board review and discussion. Observations of the FDA inspection and the response of the principal investigator were assessed. The Board recommended approval of the investigator(s) to continue to conduct the study [or to be eligible to conduct future studies].

Other agenda items: periodic reviews/extension requests, increased enrollment requests, final reports, amendments (no risk changes), expedited reviews, periodic protocol reviews, study site approvals, site closures, complaints from participants, consideration of local ethical standards, and safety reports were presented with the recommendations by the Chairman. There being no further questions, approvals were granted in accordance with the Chairman's recommendations.

Glenn P. Lambert, MD reported to the Board the following **Expedited Reviews** for the week ending on **January 28, 2008:**

- **Other Study Sponsors & Number Omitted**

The following studies were granted **Periodic Protocol Review** approval by the Board on **January 28, 2008**:

- **Other Study Sponsors & Number Omitted**

Glenn P. Lambert, MD reported to the Board the following **Site Approvals** for the week ending on **January 28, 2008:**

- **Other Study Sponsors & Number Omitted**

The following **Conflict of Interest Statements** made by the following Investigators were granted approval by the Board on **January 28, 2008**:

- **Other Investigators, Study Sponsors & Number Omitted**

**New Business**

**(LANXESS Corporation, G4330108001A382)** The Protocol (dated 1/21/07), the Consent Form (dated 1/21/08) were conditionally approved pending incorporation of the **non-substantive** recommendations outlined in the Board letter in the study file.

- **Other Study Sponsors & Number Omitted**

Motion was called to approve or conditionally approve the studies. There being no further discussion the roll was called. Motion carried. All meeting votes were unanimous with a vote of 5:0 with a sustained quorum. There were no controverted issues and there was no conflict of interest for any of the Board members in attendance. Approvals will be for one year from date of site notification.

The meeting adjourned at **6:30 pm.**

Karen Radcliffe
Karen Radcliffe

1-30-08
1-30-08

**ICR RESPONSE TO EIRB RESPONSE**

ICR, INC
1330 Dillon Heights Avenue
Baltimore, MD 21228
Telephone: (410) 747-4500
Fax: (410) 747-4928

Protocol Amendment

| | |
|---|---|
| Project Number: | 0108-433-0161 |
| Protocol Number: | G4330108001A382 Version Date January 21, 2008 |
| | Amended as Version Date February 1, 2008 |
| Sponsor: | LANXESS Corporation |
| Test Article(s): | KBR 3023 All-Family Insect Repellent Cream and |
| | KBR 3023 All-Family Insect Repellent Spray |
| GLP Compliance: | 40 CFR 160 |
| Amendment: | Protocol G4330108001A382 version date January 21, 2008 was amended as per changes requested by Essex Institutional Review Board. These changes are incorporated in the protocol with version date February 1, 2008. |
| Impact On The Study: | These changes improve the clarity of the protocol. |

Submitted by: William J Dayton 2/4/08
Date

Acknowledged by QA: 2/4/08
Date

**PROTOCOL NUMBER:** G4330108001A382


**PROJECT NUMBER:**
0108-433-0161

**PROTOCOL TITLE:**
**EVALUATION OF THE EFFICACY OF KBR 3023 (Picaridin; Icaridin)- BASED PERSONAL INSECT REPELLENTS (20% CREAM and 20% SPRAY) AGAINST STABLE FLIES IN THE LABORATORY**

**PROTOCOL VERSION DATE**
February 1, 2008

**PROPOSED LABORATORY INITIATION DATE**

TBD
**PROPOSED LABORATORY CONDUCT COMPLETION DATE**
TBD

**STUDY DIRECTOR**
William J. Gaynor

**STUDY ASSOCIATES**
Charles Cornell, Timothy Foard, Niketas Spero, Gloria Stevens and Fouad Zgidou

**SPONSOR REPRESENTATIVE**
**G.K. Sangha**

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

**TESTING FACILITY**
ICR, Inc.
1330 Dillon Heights Avenue
Baltimore, MD 21228-1199

## TABLE OF CONTENTS

# EVALUATION OF THE EFFICACY OF KBR 3023 (Picaridin; Icaridin)- BASED PERSONAL INSECT REPELLENTS (20% CREAM and 20% SPRAY) AGAINST STABLE FLIES IN THE LABORATORY

## 1. INTRODUCTION

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 for safety, low skin penetration, 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). LANXESS is the study sponsor.

Icaridin (US EPA registration name Picaridin), the current common name, was developed under the Code Name KBR 3023 and the registered trade name Bayrepel$^{TM}$ 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. Despite this, Picaridin and KBR 3023 will be used henceforth as these names have become the most widely used ones in the U.S.

## 2. OBJECTIVE OF THE STUDY

The objective of the study is to determine the mean protection time from bites by stable flies provided by the test articles under laboratory conditions to confirm this hypothesis.

## 3. HYPOTHESIS

Two repellent products (205 formulations of All-Family Insect Repellent Spray and All-Family Insect Repellent Cream and referred to as "test articles" and "test products' henceforth) are expected to provide 8 hours or greater than 8 hours of personal protection from stable flies (also referred to as "flies") in a laboratory test. (also referred to as "study").

## 4. STUDY RATIONALE

ICR Inc. ("ICR"), located at 1330 Dillon Heights Avenue, Baltimore MD 21228-1199, will conduct the proposed test at its laboratory. This will evaluate the efficacy of two 20% KBR 3023-based insect repellent products (KBR 3023 All-Family Insect Repellent Spray and KBR 3023 All-Family Insect Repellent Cream) against laboratory-raised stable flies. Laboratory studies, such as the one proposed, have been considered by regulatory authorities and the scientific community to be a reliable method for testing the performance of topically-applied insect repellent products. Under EPA's OPPTS Guideline 810.3700 ("Product Performance of Skin-Applied Repellents of Insect and Other Arthropods") human efficacy study data is required to support registration of insect repellent products to substantiate the product label claims.

The products (20% Formulations of All-family Insect Repellent Spray and All-Family Insect Repellent Cream) are conditionally registered by EPA pending conduct of new efficacy data including stable flies. However, no testing of 20% KBR 3023 products has been conducted against biting flies in the US or Europe. A 7.5% KBR-3023 is the highest level tested in a field and a cage study conducted in Europe, but it involved three species which do not occur in the U.S., as well as stable flies, (unpublished LANXESS study 06-LX-04, 2007). The study duration was limited to only four hours and the details of the data are not available. Therefore, this study is planned to determine the efficacy of the two 20% KBR 3023 products in a cage test.

Stable flies can transmit animal-related diseases, but very rarely transmit any diseases which afflict people. The pest status of these flies as they relate directly to humans is almost entirely due to their painful bite and annoyance. They are rapid fliers and easily elude the swatting hand or rolled newspaper. The data generated from the study will provide consumers with an alternative and effective choice of a repellent.

## 5. RISKS AND BENEFITS

The main risks associated with the proposed study are the potential for allergic or irritation responses to the test materials, and exposure to biting flies. The potential for disease transmission is almost non-existent. Risk to the subjects health and safety are not likely either during or after the study as described below:

Most people do not exhibit a skin reaction to stable fly bites other than feeling transient pain. ICR's stable flies have been raised in the laboratory for many generations and have not been exposed to human blood sources (they are fed *in vitro* on bovine blood). Therefore the potential risk of contracting an insect-borne disease will be essentially zero, leaving irritation from stable fly bites as the only hazard from these insects.

Picaridin has low acute toxicity and long term studies showed no adverse effects of concern by the use of the product. The product has been registered in 33 countries and over years of use showed that it can be used safely (the safety profile of the product, as provide by the sponsor, is presented in Appendix V). The 20% concentration of the active ingredient in the two All-family formulations proposed for the study is higher than the marketed and EPA-registered formulation. The product will be used according to current label and risks associated with the use during the study are not anticipated.

The inert ingredients used in the two products have been used extensively in the cosmetic industry without adverse events. Subjects with a history of reaction to insect bites, insect repellents, and skin care products will be excluded from the study. Further, the subjects will be closely monitored during both the dose-determination phase of the study, as well as during the repellent phase of the study, for signs of reactions. Subjects will be especially closely monitored during the dose-determination study when they apply the products to their forearms (see *Dose Determination*). Prompt medical attention will be sought should any adverse reaction be experienced.

## 6. STUDY OVERVIEW

There will be two phases of the study: the dose determining phase and repellent phase.

*a) Dose Determination Phase*
The test doses will be determined before the repellent test by allowing human subjects to apply both products to their forearms. These subjects will be instructed to apply the products as they would normally when applying a repellent, the only criterion being that the amount applied is what they would choose. ICR will measure the weights applied. Each subject will apply each product three times. The means of these application weights will be used to treat the subjects in the repellent test. This is detailed below under section 11 (page 17)

b) *Repellent Test Phase*
ICR plans to test 12 human subjects, with their left forearms treated with the cream product and their right forearms with the spray products, for repellency to groups of 25 caged stable flies. Subjects will expose their treated forearms to these flies for 5 minutes every half hour for 10 hours, or until they receive a confirmed bite on both arms, whichever occurs first. The times to the first confirmed bite will be the protection time for each product on each subject. Ten hours will allow a reliable documentation of an 8-hour claim. This phase is detailed below under section 20 (page 22).

## 7. TEST ARTICLE (PRODUCT) NOMENCLATURE, INFORMATION AND DISPOSITION

a) *The table below summarizes the identity of the two test articles.*

| Active Ingredient | Product Name | EPA Reg. No. | Application Rate | ICR Code |
|---|---|---|---|---|
| **20% Picaridin*** | **KBR 3023 All-Family Insect Repellent Cream** | **39967-50** | ≤4 mg/cm$^{2*}$ ≤1000 mg/250cm$^{2*}$ | **A** |
| **20% Picaridin*** | **KBR 3023 All-Family Insect Repellent Spray** | **39967-53** | ≤4 mg/cm$^{2*}$ ≤1000 mg/250cm$^{2}$ | **B** |

* 2-(2-hydroxyethyl)-1piperidinecarboxylic acid 1-methylpropyl ester

b) Upper limit for treatment dose
The amount to be applied will be determined in the dose determination phase of the study, but in no case will it exceed 4 mg/cm$^2$ without additional review and approval by EIRB as this is the maximum application rate that they will be provided for the purpose of hazard assessment.

c) MSDS
A Material Safety Data Sheet (MSDS) shall be provided for each test, control, and/or reference sample, which will include any hazardous information of the test articles. The percentage of all active ingredients and any hazardous constituents must be included in all MSDSs.

d) *Chain of custody letter*
A chain of custody letter must accompany all test, control, and/or reference test articles.

- **e)** *Test Article Characterization*
  Sample characterization is a key GLP (Good Laboratory Practices) requirement detailed in 40 CFR Part 160. The sponsor is solely responsible for conducting the complete test article, control sample, and any reference sample characterizations according to GLPs, and for providing ICR with this characterization data prior to the experimental start date of this study. This characterization must define the identity, strength, purity, and composition of the batch(es) or lot(s) of test articles. If any of the test, control and/or reference test articles are currently available for consumer use and/or purchased in the marketplace, ICR will need the same characterization information provided by the sponsor prior to the experimental start date of this study. If documentation of this characterization is not provided prior to the experimental start date, this will be noted as a

non-compliance item in the GLP compliance statement. This sample characterization information will be retained in the ICR archives, and a statement identifying this location will be included in the final report. LANXESS has agreed to provide this information.

f) *Sponsor Responsibilities*
The study sponsor shall provide the study director with the entire compositions of the test articles prior to the experimental start date.
The stability of the test and, when applicable, control, and/or reference test articles shall be determined by the sponsor prior to the experimental start date. When relevant to the conduct of this study, the solubility of each test, control, and/or reference sample shall be determined prior to the experimental start date.

Methods of synthesis, fabrication, or derivation of the test, control, and/or reference test articles shall be documented by the sponsor, and the location of such documentation shall be specified by the sponsor in a letter to the Study director. LANXESS has done this.

The stability of test, control, and/or reference test articles stored under the test site conditions shall be known for all studies. LANXESS has this information.

g). *Return of Unused Test Articles*
All unused portions of the test articles will be returned to the sponsor within 30 days of the final report being sent to the sponsor. The sponsor will be responsible for all costs for the return of the test articles, including any costs associated with hazardous materials shipping.

## 8. TEST ORGANISM

*a) Introduction*
The stable fly (*Stomoxys calcitrans* L) resembles the better known house fly (*Musca domestica* L.). Close inspection reveals that it has the piercing mouthparts (proboscis) of a blood-feeder rather than the enlarged, rounded tip of the house fly's mouth parts (which is used for swabbing up food). Stable flies are obligate blood feeders with both sexes relying upon this diet (unlike mosquitoes in which only the females will take blood meals). Stable flies attack cattle, horses and other farm animals, household pets and people. Their bite is painful, often more so than that of a mosquito. The itching and swelling which often follows a mosquito bite, is however, usually lacking after stable fly bites. They are restless biters and will often interrupt a meal to fly elsewhere. As noted below stable flies rarely, if ever, transmit diseases to humans but they have been implicated in diseases to animals (e.g. anthrax and the equine nematode parasites of the genus *Habronema).*

*b) Origin of ICR Stable Fly Colony*

The source of ICR's stable fly colony is the colony maintained by USDA Gainesville, Florida. Pupae from this colony were obtained in November 2006. Prior to this ICR had maintained a stable fly colony originating from USDA Kerrville Texas in 1983.

c) Stable Flies for Repellent Study

Groups of twenty-five adult, mixed sex, 3-10 day old stable flies will be aspirated from stock cages and released into each cage for each 5- minute exposure period. These test stable flies will have been fed 10% sucrose rather than their normal diet of citrated bovine blood. They will have had no sucrose for twenty-four hours prior to the study and they will have not have received a blood meal.

## 9. TEST CAGES

a) *Description*

There will be six test cages and two subjects will use each cage. The aluminum test cages (constructed by ICR) measure 2 x 2 x 2 feet with two sleeved entry ports on each of two opposite sides of the cage (4 entry ports/cage). The cage sides (except for the sleeved entrances) and top are screened. The floor is lined with a reflective material to facilitate observation of stable flies landing on the under surfaces of the forearms. A bar runs across the center of the cage to serve as a hand rest. See figures 1 and 2 below.

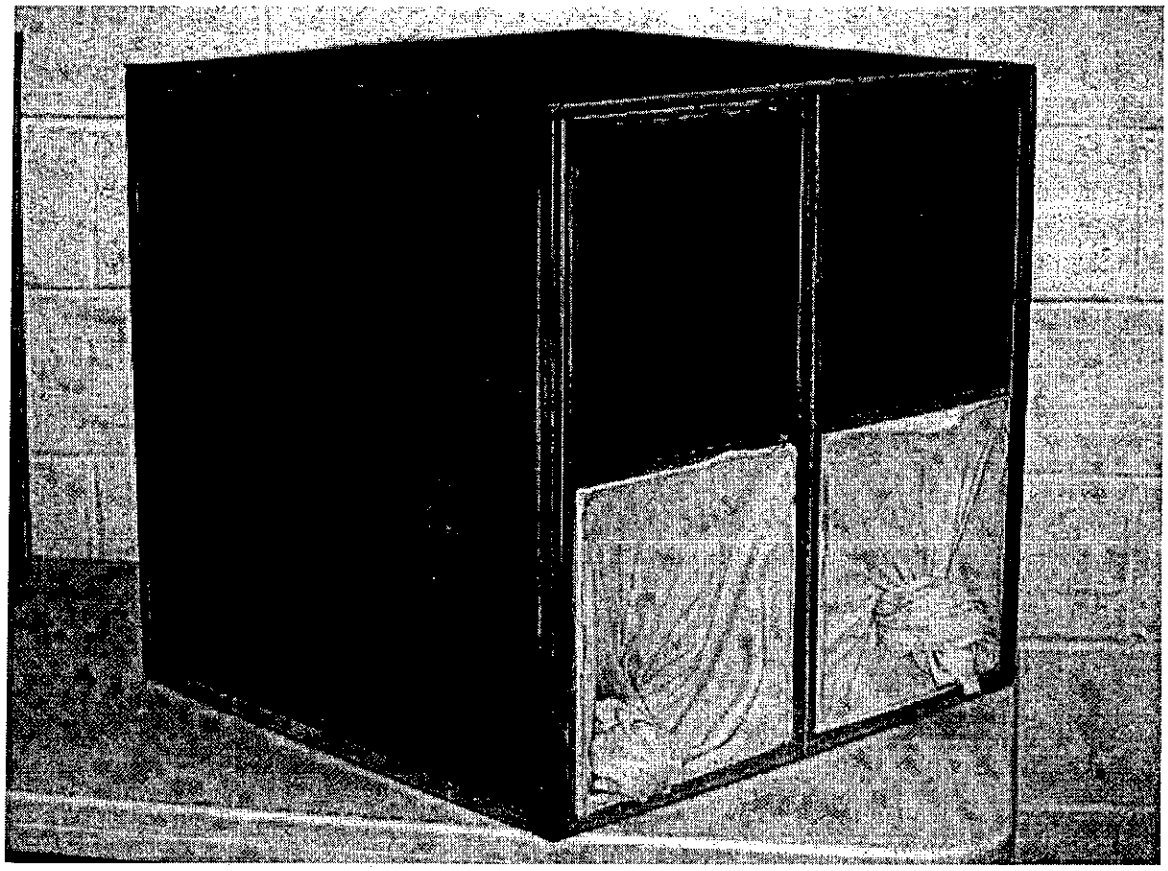


Figure 1. Test cages showing entrance sleeves closed

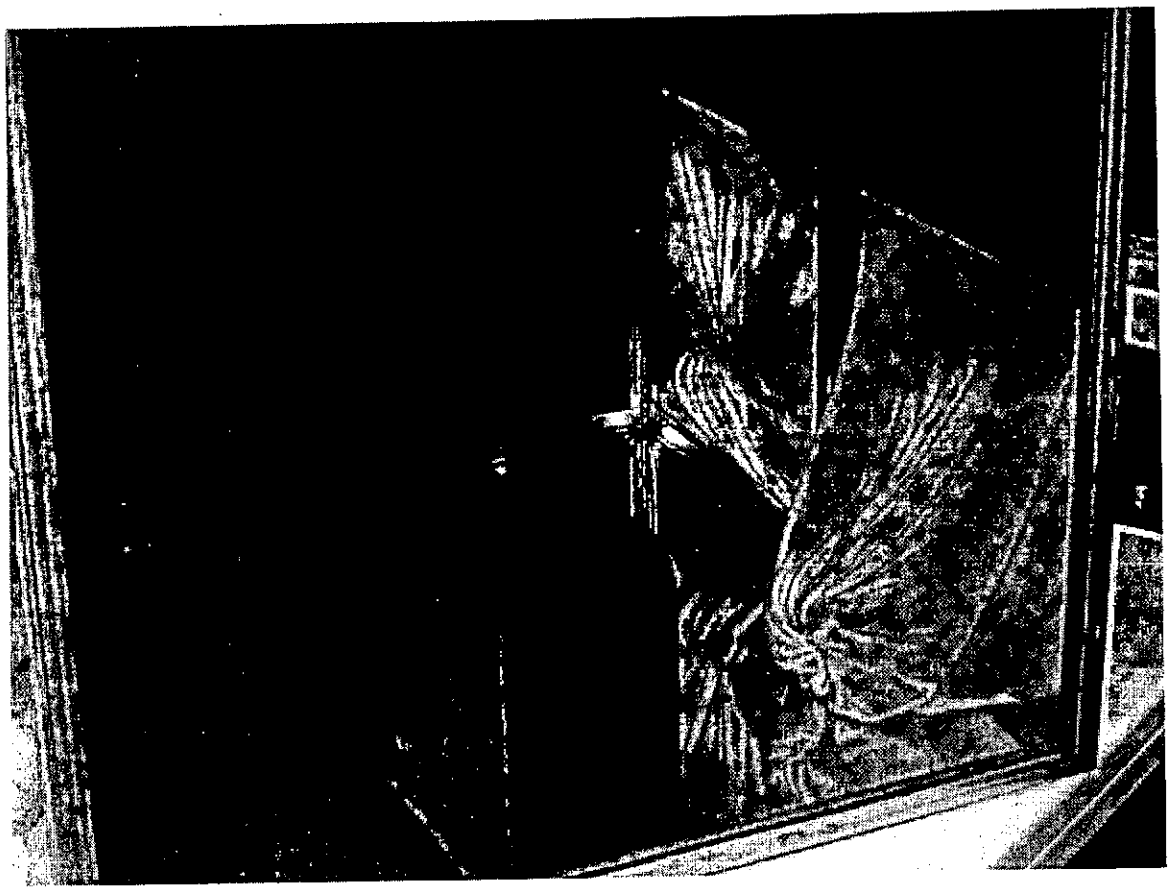


Figure 2. Test cages show hand rest bar and reflecting mirror.

*b) Evidence for Lack of Interference between Two Subjects' treated Forearms in Cages*
ICR has tested pairs of subjects in these cages with mosquitoes or stable flies for over 30 years and has not seen any evidence of interference between different treatments. Evidence of this lack of effect is provided by incomplete treatments or abrasion of treated forearms. In the former, if a 250 $cm^2$ area of a forearm is incompletely treated such that areas of skin are left untreated, stable flies will promptly land on these areas, despite the close proximity of treated skin. Similarly, ICR has seen cases where subjects have accidentally rubbed their treated forearms against their sides or another object, removing some of the product. Stable flies will often land on these abraded areas before the nearby unabraded areas.

## 10. USE OF HUMAN SUBJECTS

### a) Introduction

There are currently no viable alternatives to using human subjects to determine the efficacy of insect repellents. Under the Federal Insecticide, Fungicide and Rodenticide Act ("FIFRA"), EPA requires that efficacy data collected from human studies be submitted to register for insect repellents. These data must substantiate any public health protection claims made on the product's labeling. Specifically, data are required to both substantiate the repellency of specific insect pests and inform the user how long the products will repel the pests on the label.

While there is an economic incentive to the sponsor of the study to offer a new insect repellent alternative to consumers, such products must benefit consumers or these products will not be purchased or used. It is important to bring new insect repellent products to market so that consumers have alternatives that are effective, acceptable and convenient to use. The products to be tested in this study have been formulated to provide protection from stable flies and to be easy to apply, pleasant to use and offer alternatives to those containing other repellent active ingredients, such as DEET.

ICR will evaluate repellency based on protection from bites while conducting laboratory studies to try to minimize discomfort to the test subjects. Efficacy is defined as the Protection Time (PT). The PT is the time interval between the application of the repellent and the First Confirmed bite (FCB). A stable fly inserts its proboscis into the subjects' skin – an act which is both felt by the subject and observed by an ICR staffer. The FCB is a bite which is followed by another bite within 30 minutes.

This study is intended for submission to EPA to support an insect repellent label claim for stable flies. The results obtained from the study will enable the product to be used worldwide if repellency is demonstrated.

### b) Justification for use of human subjects

Human subjects are required for this study because there are no satisfactory substitute models for testing insect repellents. EPA recognizes this in its draft OPPTS Guideline 810.3700 which require testing of repellents on human subjects. While there has been experimental work on product repellency using animal models, such as mice and guinea pigs, the data are not a sufficiently reliable predictor of performance on humans.
It needs to be noted that animal testing has its own set of ethical concerns, including the impossibility of obtaining informed consent from the animal subjects.

**c) Recruiting pool**

ICR is located in Baltimore County, Maryland. According to the 2000 Census, the racial makeup of Baltimore County 74.39% white, 20.10% black or Afro-American, 0.25% Native American, 3.17% Asian, 0.03% Pacific Islander, 0.62% from other races, and 1.43% from two or more races.

**d) ICR's Pool of Candidate Subjects and Plans for Representative ness**

ICR's current pool of potential subjects are all white. Afro-Americans and North Africans have participated in previous studies. For the proposed stable fly test, ICR will look for recruits from the Afro-American community, as well as from the white majority population to correct this slight imbalance.

**e) Selection Criteria**

*Inclusion Criteria:*

| | |
|---|---|
| Number: | 12 test subjects and one negative control subject needed |
| Sex: | Male or Female |
| Age: | 18 to 70 |
| Race: | No exclusions |
| Literacy: | Must be able to read, speak, and understand English |

*Exclusion Criteria*:

1. Test subjects cannot participate if they are pregnant or breastfeeding.
2. Test subjects cannot be an employee or a relative of an employee of ICR Inc., the sponsor, or any other interested party.
3. Test subjects must follow the requirements of the study as explained to them.
4. Test subjects must not be known to be unduly sensitive to stable fly bites (this is not an exclusion from the dose determination phase of the study)
5. Test subjects must have no known sensitivity to insect repellents or skin care products.
6. Test subjects must be attractive to stable flies, as evidenced by previously being bitten by stable flies (optional for dose determination)
7. Test subjects must not smoke or drink alcoholic beverages 12 hours prior to the test.
8. Test subjects must not use perfumed cosmetics, skin creams, shaving lotions, etc. after 8 P.M. the night before the test, and during the test.

ICR complies with the EPA's Final Rule governing the use of human test subjects, and adheres to 40 C.F.R. Part 26 Subparts K and L when it uses human subjects in studies.

**f) Institutional Review Board**

All EIRB documents will be submitted to EPA/HSRB as a package separate from the protocol. ICR uses the following institutional review board ("IRB"):
Essex Institutional Review Board, Inc. ("EIRB")
121 Main Street
Lebanon, NJ 08833

This IRB is accredited by PHRP (Partnership for Human Research Protection Inc.), and is currently in the process of obtaining accreditation from AAHRPP (Association for the Accreditation of Human Research Protection Programs).

Approval of all documentation for human subject testing must be obtained from EIRB, EPA, and the HSRB before such testing can occur.

**g) ICR's Use of Selection Criteria**

ICR has developed a pool of male and female test subjects. The test subjects ICR recruits represent a diverse group including retired teachers, business owners, contractors, engineers, as well as students, homemakers and others.

ICR will exclude pregnant and breast feeding women from this study due to ethical concerns. ICR will also exclude children under the age of 18 for the same reason. Individuals unable to read, speak, or understand English will be excluded to ensure that all test subjects understand the ICD and test parameters. Employees or relatives of employees of either ICR, the sponsor, or other interested parties, will be excluded to avoid the possibility of coercion. Individuals sensitive to stable fly bites, insect repellents, or skin care products will be excluded to avoid placing them at risk. Although these groups of people that ICR would exclude are groups of people who would probably use repellents, their exclusion is justified because this will protect them from potential hazard.

ICR's list of potential test subjects is as representative of potential repellent users as ICR is able to make it in terms of both practical and ethical considerations. ICR test subjects need to be in good health to withstand the rigors of the specific test. In the case of this laboratory test, the rigors will be very minor – boredom is likely to the main one. ICR will accept individuals between the ages of 18 and 70. This age group represents a large portion of the US population who would encounter stable flies and have a need to use insect repellents. Since there is no risk of arthropod-borne disease, exclusion of individuals over 55 is not justified.

ICR will select individuals from its database of candidate test subjects. This will be accomplished by drawing numbers that correspond to the candidate subjects. ICR will attempt to select even numbers of male and female test subject (6 female and 6 male in this test) to

eliminate any gender bias in this test. The reason for this is that gender has been shown to affect attractiveness of the subjects to mosquitoes and the same may be true of stable flies.

**h) Consenting**

All candidates will review and sign an Informed Consent Document ("ICD") prior to acceptance as study subjects. The ICD will be formally explained to all candidates before the study is scheduled to begin. A candidate may visit ICR to review and sign the ICD or the ICD can be mailed to the candidate for their review. If mailed, the study director will phone the candidate to answer any questions regarding the ICD. If any candidate refuses to sign after learning the details of the document, they will not be allowed to participate in the study. After the ICD is fully described to the candidate, he or she may then sign the ICD in the presence of an ICR staff and a copy of the ICD will be made and returned to the candidate. He or she will then be notified within one week if they have been enrolled as a subject in the study. The Informed Consent Document will have been approved by an Institutional Review Board before it is presented to the candidates for the study.

**i) Remuneration**

For the dose determination part of the study, the subjects will be paid $11/hour for a 9 hour day even though the duration of this part of the study is likely to be less than 4 hours per subject.

For the repellent part of the study, the subjects will be paid $11/hour for the first 9 hours and $17.50 for each additional hour they spend on the day of the study. The study will last about 10 hours with approximately one hour of preparation time for a total of 11 hours. A total payment of $134 will be paid to each test subject for the day. If a subject drops out of the test at our request but they have complied with all of our requests, they will receive full payment. If the subject drops out of the test either at our request because they have not followed all of our directions, or they just choose to drop out, they will be compensated for their time up to that point at the rate of $11 per hour.

Payments will be mailed to the subjects on the 15$^{th}$ or 30$^{th}$ of the month.

**j) Recruitment Procedures**

ICR has been conducting repellent studies for over thirty years. During this time ICR has amassed a large list of potential subjects. Some of these subjects refer friends and colleagues to ICR. When a repellent study is planned, ICR will contact candidate subjects in its data base by telephone and briefly discuss the study. Any study specific inclusion/exclusion requirements will also be mentioned at this time.

ICR will use a recruitment script to recruit test subjects for this study,☹ (Appendix VI).

If the candidate is interested and is available, the inclusion/exclusion criteria will be discussed in more detail to determine if they qualify to participate. The ICD will also be discussed with them at this time. In addition, ICR will mail a copy of the ICD to each candidate for their review. They will be instructed to contact the study director to verify receipt of the ICD and to ask any ICD or study-related questions they may have.

The study director will contact all candidate subjects by phone several days after their receipt of the ICD to make sure that all their questions have been answered. All candidates will be offered the opportunity to come to ICR to go through the consent process in person. If contacted individuals choose to visit ICR office, they may voluntarily sign the ICD if they wish to be enrolled in the study. If they choose not to visit ICR's office prior to the study date, they must sign the ICD on the study day before taking part in the study.

Any candidate who declines to sign the ICD will not be permitted to participate in the study.

There will be no coercion for any candidate to participate. The inclusion/exclusion criteria are clear, the payment is simple; the candidates will be informed of the conditions they will likely encounter and what is expected of them.

Each female candidate will be informed that if they sign the ICD and want to participate in the test, they will be required to perform an over the counter pregnancy test on the morning of the study. The test results will be confirmed by a female ICR employee and the study director. Once they have signed the ICD, each consenting test subject will be informed that they may drop out of the study at any time without penalty (except that they will lose some of their potential remuneration, based on the time they miss). Further, they may leave as soon as practical after early withdrawal from the test.

**k) Pregnancy Testing**

After signing the ICD and shortly before any treatment with a test articles, each female candidate will take a pregnancy test as described by the label of an over-the-counter pregnancy test kit supplied by ICR. This will apply to the dose determination phase (section 11 below) and to the repellent test phase (section 20 below). Any subject who shows a positive result will be discretely excluded from further participation. The presence of multiple female subjects will allow the reason for their exclusion to be kept private. A female ICR staff member will confirm the pregnancy test results. The study director will be advised of the results, but no one else will be. The reason for the positive subject's exclusion from the study will be kept private by the study director informing the other subjects that this subject has not been able to meet one of the inclusion or exclusion criteria, without specifying which one.

## 11. DOSE DETERMINATION

### a) Introduction

The label directions on insect repellents provide general instructions on how much product to apply, but consumers may ignore these instructions or the instructions may be too vague to instruct the consumer adequately. The proposed study will include a dose determination phase before the repellent test is conducted. This will allow the products to be tested at rates which consumers are likely to use. Therefore 12 subjects will be recruited, as described above, to determine typical consumer doses for both products.

### b) Preparation of Subjects

ICR staff will measure the subjects' forearms and demarcate 250 $cm^2$ areas for treatment, as described subsequently, under *Personnel Preparation.*

### c) Separation of Subjects

It is important that subjects are not able to observe or converse with each other before or during application of the products as this could bias them as to how much they would apply. Therefore each subject will move to a separate room with an ICR staff member present before treatments begin.

### d) Applications of Cream Product

The subjects will be given a copy of the label for the cream product and a sample of the cream. They will be asked to apply the cream, according to label directions, to their forearm, using their gloved hand, until they have applied what, in their opinion, is enough. The weight of product applied will be calculated by weighing the product container before and after application. Subjects will then wash off the cream using soap and hot water, dry their arms and repeat the process for a total of three applications.

### e) Applications of Spray Product

The subjects will then be given a copy of the label for the spray product and a sample of the product itself. They will treat their forearms with the spray. They need to be able feel the spray hitting their skin in order to decide when enough has been applied, but some of the spray droplets will blow by their forearms, making accurate measurement of the dose applied difficult. Therefore a different method is called for. An approximately 5 cm wide band of water proof surgical dressing will be wrapped around the central part of each forearm with the impervious layer against the skin and secured by two rubber bands. A layer of gauze, or other absorbent material, will be wrapped around the dressing to provide additional absorbent capacity. The subjects will then spray their forearms until satisfied that enough has been applied. The dressing, gauze and rubber bands will be weighed before and after to determine the weight applied per unit area and converted to the weight to be applied per 250 $cm^2$. This procedure will be repeated for a total of three applications.

**f) Calculation of Dose**

The weights of the cream and the spray product will be averaged per subjects (mean of three applications per product). Then an overall mean will be calculated for all subjects for each product. These overall means will be the doses to be used in the repellent test with stable flies. The standard deviation and standard error of the mean will be calculated for each product across all subjects to determine the spread of application rates in this small sample of the general population.

## 12. NEGATIVE CONTROL

One subject will be selected to be the negative control. Selection will be by a drawing of numbers. One untreated arm of the control subject will be used to establish the aggressiveness of each cage of 25 stable flies.

Twenty five stable flies will be added to each cage at the start of test. The control subject will insert his/her untreated forearm into each cage and leave it there until two stable fly landings have occurred. An ICR staffer will gently push landing flies off the control subject's arm before they can bite by reaching in with a protected hand from a port on the other side of the cage with a wooden applicator stick. This approach will be needed since stable flies, unlike mosquitoes, can cling too tightly to a subject's arm to be easily shaken off. ICR staff will record the time when two landings occur.

If fewer than two stable flies land in 60 seconds in any of the six test cages, all stable flies will be vacuumed from all six cages and a new group of twenty-five stable flies will be released into all six cages.

No comparison will be made between the control landing rate and the treated subjects.

## 13. RATIONALE FOR NOT HAVING POSITIVE CONTROLS

Firstly, EPA is not requiring positive controls. Secondly, sufficient biting pressure (as evidenced by at least two landings in 60 seconds in a 250 $cm^2$ area on an exposed untreated control arm) will be confirmed at the start and throughout the study before each exposure period. Thirdly, a positive control group would not confirm the stable fly repellency of the test product nor would it help in determining a reliable protection period for these products under laboratory conditions. Finally, putting additional subjects at risk, however minimal, would be unethical.

## 14. SUPPORT STAFF

Additional ICR staff members will support the study director and test subjects in their activities These ICR staff members, along with the study director, will record all test data. Test subjects will not record any data. ICR staff are trained in the procedures to be used in this test and are familiar with ICR's SOPs. The quality of the study results could suffer and these results would be difficult to defend in one of the routine an EPA audits which ICR is subject to. The same difficulty would apply to a court of law if untrained test subjects recorded data.

## 15. MISCELLANEOUS SUPPLIES

Syringe, (minus the needle), micropipette and tips, Q-tip®s, latex or vinyl gloves, clip boards, data record forms, scissors, elastic bandages, water proof surgical dressing, gauze, rubber bands, Elastikon® tape, pencils, marking pens (e.g. Sharpie®), hygrothermograph, unscented Neutrogena® soap, paper towels and a stop watch, Caladryl® or Calamine® lotion.

## 16. RECORDS TO BE MAINTAINED

All study notes, data collection sheets (true copies), SOPs (originals), Chain of Custody letters (true copies), Sample Log and Sample Record of Use Forms (true copies), the protocol (true copy) and signed Informed Consent documents will be maintained in the ICR archives. Original documents will be provided to the sponsor for archiving with the exception of SOPs, Master Schedules, signed Informed Consent documents, test article characterization, and personnel files.

## 17. RISK CHARACTERIZATION AND MINIMIZATION

The subjects will be exposed to two types of risk:

1. *Test products.*

These proposed insect repellents use the active ingredient, Picaridin, which was registered by the US EPA under FIFRA on December 7, 2000. As required under FIFRA, registration of Picaridin is supported by an extensive data package that includes toxicity test data that demonstrate low acute and chronic toxicity. The EPA "New Pesticide Fact Sheet" for Picaridin indicates that its toxicology data base is complete and no additional studies are required. This active ingredient has been used without significant incident by the study sponsor and other insect repellent companies and many consumers. All of the inert ingredients used in the finished insect repellent products have a long history of safe use in various cosmetics.

For registered products containing Picaridin®, the EPA risk assessment assumes that each application of insect repellent products is to a skin surface area of 4,538 $cm^2$ for adults. In the proposed test, the product will be applied once to the subjects on the test day over a surface area of only 500 $cm^2$ (*i.e.* 250 $cm^2$ on each forearm). Consequently, the test subjects in this study will only be exposed over an area of approximately 11 percent of that previously reviewed and approved by EPA for products with the same Picaridin® concentration. Further, the label directions of these registered products allow for up to two applications per day, while the efficacy study will employ only one (however the dose determination study will involve three or occasionally, four applications). A minimum 100-fold margin of exposure (MOE) is considered to be the target for the determination of acceptable risk from systemic exposure. The MOE is based on the No Observed Adverse Effect Level (NOAEL) for systemic effects, the concentration of active ingredient in the formulation, frequency and rate of application, skin surface area and body weight, and dermal absorption. The MOE for the test subjects in this efficacy study will substantially exceed the minimum 100-fold target and is, therefore, considered acceptable under widely recognized scientific standards.

While there is little concern for the test articles to induce an adverse reaction in the test subjects, they will be monitored throughout the study and prompt medical attention will be obtained if any adverse reaction is observed among the subjects in the test. Those individuals who are known to have allergies to stable fly bites, insect repellents, or skin care products will be excluded from the study.

2. *Bites from stable flies.*

The principal effect of a stable fly bite is a sharp but transient pain. In most cases, stable fly bites do not lead to the itching and localized swelling which are the typical aftermath of mosquito bites. A few people may experience a small area of redness, swelling and itching that usually goes away within 24 hours. In extremely rare cases, a serious reaction to a bite may result in swelling of the throat, hives and wheezing. This condition (anaphylaxis) could be life-threatening and requires immediate medical attention. All subjects known to have severe reactions to stable fly bites will be excluded from this study.

All subjects will wear latex or vinyl gloves. Only a small portion (250 $cm^{2)}$ of bare skin on each arm will be exposed. All other parts of the body will be covered with the subject's personal clothing. This will protect them in case of any escaped flies. Immediately upon receiving a FCB on an arm, that arm will be withdrawn from the test and not be exposed to the caged stable flies again. Caladryl® or Calamine® lotion and rubbing alcohol will be available for use to mitigate any reaction to stable fly bites.

An ICR staffer trained in First Aid will be on site, and First Aid supplies will be available. A selected local hospital will receive prior notification of this study and on-site staff will have cell phones to make emergency calls if necessary. In the case of medical emergency, people will be

transported to the selected local hospital, St. Agnes Hospital, by either ICR staff or ambulance. The hospital is 7 miles from ICR, at 900 S. Caton Ave., Baltimore, MD. 21229. The telephone number of the ER center is 410-368-2000. If any test subjects need medical attention, their medical care will be paid by ICR.

*Arthropod-borne diseases*

As noted previously, there will be no risk for arthropod-borne diseases from the stable flies used in this study. Stable flies are known to carry human diseases only very rarely, if at all. More importantly, this strain has been reared in the laboratory for many years and has not been allowed to feed on human blood (bovine blood is used). Owing to the forgoing factors, transmission of a blood-borne disease by these stable flies is not possible.

Finally, the subjects will only need to receive two bites within 30 minutes to confirm breakdown, after which the test arm will not be exposed to flies again, thus minimizing their exposure to the flies.

## 18. DISCOMFORT AND HAZARD

The stable flies being used in this test are not capable of transmitting diseases in the wild. This strain of stable fly has been laboratory colonized for many years and has not been exposed to outside blood sources while at ICR. None of the stable flies used in this test will have had a blood meal prior to their introduction into the test cages. Once a group of stable flies has been used in a study, it will not be re-used in another study. All stable flies used in the study will be destroyed either through freezing or carbon dioxide. Transmission of a blood-borne disease by this strain of stable fly is not possible.

In the event that study related injury or illness should occur, test subjects would be instructed to seek medical attention through a health care provider, at ICR's expense. Test subjects would be instructed to submit study related bills to ICR for payment. ICR will incur the cost of any such study-related bills. The study director will contact all test subjects by telephone, two weeks after the conclusion of the study, to inquire if they have experienced any adverse effects.

## 19. BENEFITS

The sponsor will gain the most benefit from this study through knowledge gained on the performance of its repellent products. Indirect benefit may accrue to society at large by the development of more effective, safer and 'pleasant-to-use' repellent products, and alternatives to DEET-based products.

## 20. REPELLENT TEST METHODS

**a) Experimental Design**

The purpose of this study is to determine the extent to which a stable fly repellent is effective in preventing bites on exposed human skin. The repellent will be considered degraded if either of these two conditions is met: a) two stable fly bites are noticed in a single 5 minute observation period; or, b) a single bite in two adjacent observation periods is noted. The goal of the study is to provide an estimated length of protection time that a specific repellent provides.

Individuals will have repellent applied to a specific area of their forearms. Then, their arms will be exposed to live stable flies for five minutes. If two bites are noted in this time period, the case will be considered a "bite". If no bites are noted, the arm will be removed and re-exposed 30 minutes later for another 5 minutes. This process will continue either until two bites are noted or 10 hours have elapsed. The 250 $cm^2$ delineated areas on the arms of subjects will be treated and used as test areas. Only arms are being treated in this study, since arms are easy to monitor for stable fly activity. Therefore there will be twelve test arms for each treatment. Each test subject will have one arm treated with the cream product and the other arm will be treated with the spray product. ICR staff will know the identity of the treatments, but the test subject will not.

**b) Rationale for Sample Size : Number of Subjects**

The EPA draft Guideline OPPTS 810.3700) currently (1/2008) on EPA's website recommends 10 test subjects to document a protection time greater than 5 hours. Because of the high cost of doing repellent studies and the need to avoid unnecessary exposure to subjects, it is prudent to ensure data is collected from the minimum acceptable number of subjects. Therefore the target number of test subjects in the study is twelve, which includes two additional subjects in case of drop outs or ones failing to meet an exclusion or inclusion criterion on the day of the test. There will also be one negative control subject.

The choice of 12 subjects is discussed further in DATA ANALYSIS (section 23).

**c) Test location:**

This test will be conducted in the laboratory at ICR. The laboratory is maintained at ambient relative humidity and 70° F ± 15°F. These are the same conditions as the stable flies are reared under so their activity should be unimpaired; there is no need for elevated humidity as is the case with mosquitoes.

**d) Dose**

The dose will have been determined from the dose determination part of the study conducted prior to the beginning of the repellent test (see *Dose Determination* above). This dose must be

no greater than 4 mg/cm$^2$. If it is greater, an additional approval will be needed from EIRB before the repellent test can take place, since 4 mg/cm$^2$ has been given to ERIB as the upper limit for their evaluation.

**e) Blinding of the Study**

The test articles will be coded as "A" (cream) and "B" (spray). During the test these codes will be the only test article designation referred to or that the test subjects will see. The study director and members of the ICR staff will know the actual test articles, but will refrain from such identifications in the presence of test subjects. It should be noted however that the different appearance and texture of the cream and the spray will probably be apparent to the subjects.

**f) Treatment Groups and Subject Selection**

There will be two groups: a treated group of twelve (two more than required to allow for drop outs) subjects whose arms will be treated, and one untreated (control) subject whose arms will be untreated. Subjects will be given a subject number. They will be assigned to the groups by lottery selection of the subject number.

**g) Personnel preparation**

All subjects will have reviewed and signed an ICD before acceptance as a test subject participant.

i) *Pregnancy Testing*

All female subjects will conduct a urine pregnancy test on the morning of the test before any treatments. This procedure was described under section 10k.

All test subjects will then wash their arms with unscented Neutrogena® soap. The test subject's arms will then be measured in the following manner for the demarcation of the 250 cm$^2$test area:

*ii) Measurement of 250$^2$ cm areas*

The determination of the 250 cm$^2$ area of each subjects' forearms is based on the assumption that they approximate a truncated cone shape. The subject's elbow will be placed on a tabletop with the forearm held perpendicular to that surface. A mark will be made on the upper forearm 3 inches from the tabletop. A second mark will be made on the lower forearm at a point just below the wrist bone. The circumference of the arm will be measured at each of these points. The average of the two circumferences will be calculated. This represents the approximate circumference at the center point between the two marks. A third mark will be made at the center point between the two marks. The average circumference will be divided into 250cm$^2$, the total exposed surface area required for the test. This will yield the length of arm required to be exposed. The end points of this length of exposure area will be marked on the forearm so that each end point is equidistant from the center point. The endpoint measurements from the center point will be recorded so that they may be duplicated in the test. The distance from the tip of the

little finger to the center point will be measured and also recorded so that the center point may be duplicated at another time.

The above mentioned measurements will be recorded on a repellent measurement form. If a test subject has been previously measured, the existing measurements will be used.

iii) *Delineation of 250$^2$ cm areas*

The test subjects and the control subject will have 250 cm$^2$ areas delineated around their forearms and these arms will be prepared for treatment. The skin above and below the target area will be protected with elastic bandages and or Velcro® straps held in place with Elastikon® tape. Arms will be protected by shirt sleeves. Latex or vinyl gloves will be given to the subjects to protect their hands.

*iv) Determination of Attractancy to Stable Flies*

Test subjects will be checked for their attractiveness to stable flies. Subjects will place their right forearm into their cage and the number of flies landing on their arms will be counted. The required landings will be at least 2 stable flies in 60 seconds to qualify a subject as being attractive to the flies. Volunteer will repeat the qualifying exposure as above using the left arm. The procedure will be repeated if the subject fails to qualify. If a subject again fails to qualify after repeated exposures, that subject may be dropped from the study.

After qualification the test subjects will be treated with the two repellent products.

*v) Treatment*

The repellents will be coded as "A" (cream) or "B" (spray), and each arm will be labeled on the protective wrap with the code corresponding to the repellent applied. Each test subject will be treated on the right arm with repellent "A" and on their left arm with repellent "B".

The test articles will be applied to the test subjects using a syringe (minus needle), rubbed on by hand by an ICR staffer using their surgically-gloved hands. If the cream repellent is too viscous to be applied with a syringe, it will be applied with a cotton-tipped applicator stick. The amount of test article applied will be determined in the dose range finding. The hands will be protected with gloves. The control subject will receive no treatment. In the case of the spray, the product will be dispensed into a 250 ml beaker after which it will be applied by syringe (minus needle). Application of the spray will differ from the manner in which it will be used by consumers or in the dose determination phase of the study. Application by syringe is, however, required to allow accurate measurement for equal treatment.

Subjects will be treated in pairs. Both members of a pair will be treated with the cream and then with the spray. The time of treatment will be the time when the application of the spray treatment

begins. This time will represent the starting time used for calculation of the protection times afforded by the test articles.

**h) Testing**

A group of 25 stable flies will be placed in each test cage prior to the first exposure period. The aggressiveness of the caged stable flies prior to each exposure period will be determined from the landing rate on the control's arm before each test exposure. Once the landing rate has been confirmed (at least 2 landings in 60 seconds), the counts will cease. The landing rate verification will be conducted before each exposure of the treated test subjects. If fewer than the required number of stable flies land in 60 seconds, a new group of 25 stable flies will be released into that cage (as well as into the other 5 cages so as to avoid bias) after the old flies have been removed with a vacuum.

ICR staff will assist the test subjects in inserting their arms into the test cages, taking care not to rub them on the cloth sleeve. The test subjects will expose their treated forearms to the stable flies for 5 minutes. The subjects will then remove their arms from the cages with assistance from an ICR staff. Exposures to the stable flies will be repeated every 30 minutes until the treatment on any given forearm is determined to be no longer effective or until 10 hours have elapsed, whichever occurs first.

The test data to be recorded will be bites. Test data will be recorded on a Repellency Test Data Sheet.

**i) Rationale for using Bites instead of Landings as the End Point**

Bites will be used as the end point instead of landings in this test for the following reasons.

i). A fly which has been allowed to bite after it lands (takes blood into its abdomen) is less likely to land again than a fly which was brushed away after its first landing before it could bite to take blood. This fly will probably land again so it can get the blood meal it needs. This one fly could thus account for both the first landing and the second (confirming) landing. Aspirating stable flies once they land will frequently not be successful since they are elusive flyers and cannot always be captured on the first attempt by aspiration once they have landed (this was tried at ICR during protocol development). In such cases, the fly which landed cannot be identified from among the other 24 flies in the cage for subsequent attempts at aspiration. Once a stable fly has bitten and fed, however, it is much less likely to bite again as it will have accomplished its goal of securing a blood meal. Using bites therefore will greatly increase the chances that two different flies will be involved in the determination that the repellent product has lost its repellency (broken down).

ii). Unlike field testing of mosquitoes, where there is the possibility of a bite transmitting a disease, these lab-reared stable flies do not carry disease.

iii). The bite of a stable fly usually results on in transient pain only, without the ensuing itching and welting associated with mosquito bites.

iv). Stable flies in the wild usually land on one's ankles and lower legs. Therefore, if they only land and do not bite, one may not even notice them. It is only when they bite that they become a nuisance. It is more important therefore to demonstrate that the repellent prevents bites rather than landings.

v). Stable flies often land long before they bite. A conservative analysis of 9 stable fly tests conducted by ICR from 1990 to 1999 revealed that the time difference between first confirmed landing and first confirmed bite ranged from 0 to 7.5 hours with a mean of 2.6 hours. Therefore ladings would seriously underestimate the protection time for the test products.

**i. Criteria for Test End Point**

The test subjects will continue to expose their treated arms to stable flies until the FCB (First Confirmed bite) or until 10 hours have elapsed, whichever occurs first. The FCB occurs when two bites occur on the same arm in the same exposure period, or one bite occurs in each of two consecutive exposure periods (the first bite being the confirmed bite). A bite is defined as a stable fly penetrating the skin with its proboscis and taking blood into its abdomen. When the two bites have occurred as noted above, the test will terminate on that arm.
The test will be terminated on each treated arm after an FCB occurs. The subject will then be able to remove the bandages and tape, scratch and wash that arm. If they want to, they can use rubbing alcohol to help stop any itching from bites they have received. Caladryl® or Calamine® lotion may also be used. When the testing is terminated for the first arm, the subject will roll down their sleeve on that arm.

If a single bite occurs without a confirming second one within that exposure or the following one, that bite will not count towards product breakdown – two additional bites, within one or two consecutive exposures, will be required.

## 21. CONFIDENTIALITY

The information obtained from test subjects taking part in this test may be used by ICR and its sponsor and may become part of a report. This report will be kept as confidential as possible under local, state and federal law. The test subjects' first and last initial and their dedicated identity number only may be referenced. ICR cannot guarantee that the subjects' identity will be kept confidential. Essex Institutional Review Board has the right to review the subjects' records.

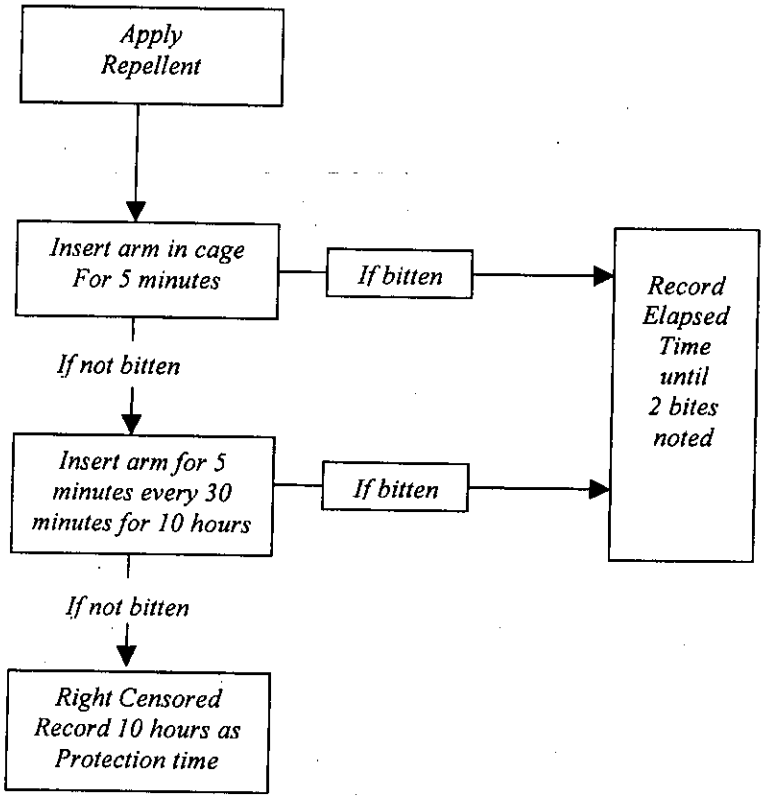
## 22. DATA ANALYSIS

**a) Goals**

The purpose of this study is to determine the extent to which a stable fly repellent is effective in preventing bites on exposed human skin. The repellent will be considered degraded if either of these two conditions is met: a) two stable fly bites are noticed in a single 5 minute observation period; or, b) a single bite in two adjacent observation periods is noted. The goal of the study is to provide an estimated length of protection time from a first confirmed bite (FCB) that a specific repellent provides.

**b) Methodology**

Individuals will have repellent applied to a specific area of their forearms. Then, their arms will be exposed to live stable flies for five minutes. If two bites are noted in this time period, the case will be considered a "bite". If no bites are noted, the arm will be removed and re-exposed 30 minutes later for another 5 minutes. This process will continue either until two bites are noted or 10 hours have elapsed. The methodology is graphically presented below:




Subjects will be assessed for product efficacy every 30 minutes over the 10 hour study interval. Thus for each complete subject, there will be 20 assessments of protection efficacy (2 assessments per hour X 10 hours).

**c) Statistical Procedures:**

***Power.*** Based on a meta-analysis of mosquito studies of this type, Rutledge and Gupta (1999) provided power tables for determining the number of subjects needed to determine protection times up to 8 hours with varying confidence limits and two-tail levels of significance. Using information from their study, 11 subjects would be necessary in order to have a 95 % confidence interval for assessing protection up to 8 hours with a ± 2-hour confidence limit.

The proposed study will use stable flies as the test organism, not mosquitoes. Stable fly behavior differs from that of mosquitoes, a meta-analysis for the former species is needed for a confident prediction of the sample size needed for a reliable estimate of protection time. ICR is unaware of

any such study. We analyzed our own database consisting of 9 stable fly repellent studies conducted between 1900 and 1999 in which the numbers of subjects ranged from 2 to 10. Our consulting statistician is of the opinion that the data are inadequate for deriving a reliable power estimate table, especially as many of the protection times were left (<0.5 hours) or right (>8 hours) censored. When these data had been excluded, the remaining data did not show survival time being significantly linked to standard deviation. With these caveats and following the procedures outlined by Rutledge and Gupta (1999), he derived the table shown below for 95% confidence levels, two-tailed with a 2-hour confidence interval.

| Time (in hours) | Standard Deviation | Sample Size |
|---|---|---|
| 1 | .95 | 1 |
| 2 | 1.18 | 2 |
| 3 | 1.42 | 2 |
| 4 | 1.65 | 3 |
| 5 | 1.89 | 4 |
| 6 | 2.12 | 5 |
| 7 | 2.35 | 6 |
| 8 | 2.59 | 7 |

The table indicates that a sample size of seven subjects would be adequate. In view of the uncertainties noted above relating to this table, we have chosen to run this study with twelve subjects in an effort the minimize the risk of interpreting repellent protection from a too small data set.

**d) Analyses.**

Data will be analyzed using SPSS v. 16 software. The Kaplan-Meier (KM) product-limit technique will be used to describe and analyze the length of time to product degradation. KM allows for the presence of right censored data and provides survival proportions as well as mean survival times with corresponding confidence intervals accordingly. Because the KM procedure is based on proportions, there is no need for the underlying scores to be normally distributed. From the KM analysis we will take the mean and median survival times along with its 95% confidence interval as the final result of this study.

In the event that *all* subjects right censor (i.e., last the entire 10 hours without any bites), we will conclude, with 95% confidence, that the product can provide protection for up to 8 hours, ± 2 hours.

In the event that *more* than two subjects drop out during the study, final estimates of protection time will be made that are consistent with the power parameters stated above.

## 23. QAU AND DATA ARCHIVING

Good Laboratory Practices, as outlined in 40 CFR §160 will be followed throughout the study. The QAU representative will observe and write phase report(s) for this study. All data will be archived.

## 24. SCHEDULE OF EVENTS

| DATE | PROCEDURE |
|---|---|
| Time Zero | Test Conducted |
| At End of Test | Verbal Report |
| After The Laboratory Test Conduct | Written Report |
| After Final Report Has Been Issued | Test articles Returned |

## 25. STATEMENT OF AMENDMENT OR DEVIATION

Any amendments to this protocol must be discussed with and approved by the Sponsor. Any amendments to, or deviations from, this protocol will be documented in the final report.

Robin G. Todd PhD, BCE
Director, ICR, Inc. 2/4/08 Date

Ellen W. Quinn
QAU, ICR Inc. 2/4/08 Date

William J. Gaynor
Study Director, ICR Inc. 2/4/08 Date

G.K. Sangha PhD
Representative
LANXESS Corporation 2-1-08 Date

# APPENDIX I:
# DATA COLLECTION SHEETS

**RAW DATA COLLECTION SHEET**

SPONSOR: 433 DATE: TIME:
S D/TECH: William J. Gaynor SPECIES: S. *calcitrans*

PRE-TEST LANDING RATES

SUBJECT Initial and Number:

| TIME (SECONDS) REQUIRED FOR 2 LANDINGS | |
|---|---|
| RIGHT FOREARM | LEFT FOREARM |
| | |
| | |
| | |
| | |
| | |

Signatures of Study Associates Recording data on this sheet/date: .....
Study Director's Signature/Date .....
Test Subject's Initials/Date .....

**RAW DATA COLLECTION SHEET**

SPONSOR: 433 DATE: START TIME:
S D/TECH: William J. Gaynor SPECIES: S. *calcitrans* TEST ARTICLE APPLIED BY:

| TEST ARTCL | SUBJ ECT NUMBER: | | SUBJ ECT NUMBER: | | CONTROL SUBJECT No. :_____ |
|---|---|---|---|---|---|
| | | | | | TIME FOR 2 LANDINGS (seconds) |
| TIME (Hours) | RIGHT ARM | LEFT ARM | RIGHT ARM | LEFT ARM | |
| | BITE | BITE | BITE | BITE | |
| 0.5 | | | | | |
| 1.0 | | | | | |
| 1.5 | | | | | |
| 2.0 | | | | | |
| 2.5 | | | | | |
| 3.0 | | | | | |
| 3.5 | | | | | |
| 4.0 | | | | | |
| 4.5 | | | | | |
| 5.0 | | | | | |
| 5.5 | | | | | |
| 6.0 | | | | | |
| 6.5 | | | | | |
| 7.0 | | | | | |
| 7.5 | | | | | |
| 8.0 | | | | | |
| 8.5 | | | | | |
| 9.0 | | | | | |
| 9.5 | | | | | |
| 10.0 | | | | | |
| FAIL | | | | | |

Signatures of Study Associates recording data: .....Study Director's Signature/Date .....
Test Subject's Initials/Date _____

# Repellent Measurements–Arm

SUBJECT:

DATE:

**LEFT ARM**

LOWER ARM =

AVG = 250 cm = =
2

UPPER ARM =

CENTER POINT = DISTANCE FROM LARGE TO SMALL CIRCUMFERENCE ____cm.= 2

DISTANCE FROM CENTER POINT TO TIP OF LITTLE FINGER

DISTANCE FROM EITHER SIDE OF CENTER POINT

**RIGHT ARM**

LOWER ARM =

AVG = 250 cm = =
2

UPPER ARM =

CENTER POINT = DISTANCE FROM LARGE TO SMALL CIRCUMFERENCE ____cm. = 2

DISTANCE FROM CENTER POINT TO TIP OF LITTLE FINGER

DISTANCE FROM EITHER SIDE OF CENTER POINT

DATA TRANSFER VERIFIED BY:_____DATE:

## APPENDIX II:
## INFORMED CONSENT DOCUMENT – DOSE DETERMINATION

Test subject's initials:.....

Date:.....

**PROTOCOL:** EVALUATION OF THE EFFICACY OF KBR 3023 (PICARIDIN; ICARIDIN) – BASED PERSONAL INSECT REPELLENTS (20% CREAM, 20% SPRAY) AGAINST STABLE FLIES IN THE LABORATORY

## INFORMED CONSENT AUTHORIZATION TO PARTICIPATE IN THE DOSE DETERMINATION PHASE OF AN ICR, INC. STABLE FLY REPELLENT EVALUATION IN THE LABORATORY

**Principal Investigator: William J. Gaynor**
**Address: ICR, Inc. 1330 Dillon Heights Ave. Baltimore, MD**
**Telephone Number: 410-747-4500**
**24 Hour Emergency Number: 410-207-0415**

**Purpose of Study**

We (ICR, Inc.) have been contracted by LANXESS Corporation to conduct a research study in our laboratory on two insect repellent products containing the active ingredient picaridin, to find out how well these products repel stable flies. Before this study can be performed the dose of the two repellents to be used in the study must be determined based on how much product a typical consumer would apply to themselves. This dose determination phase of the study is the study for which we are asking you for your participation. This dose determination phase of the study will occur in the ICR, Inc. lab where the stable fly repellents will later be tested using the doses you determine today. We have prepared this Informed Consent Document (ICD) to explain this dose determination study to you so that you can make a free choice whether or not to participate.

We will review this document with you to make sure you understand what would be expected of you if you participate, and to explain the risks you would face through your participation. Please ask us about anything you do not understand. If you have come into our office to review the document, you may take it home with you if you need more time to think about whether to participate.

We will apply the eligibility standard listed below to determine if you qualify to participate in the study. If you qualify, we will ask you to consider signing this document to indicate your consent to participate. Your signing indicates your willingness to participate in this study, but you would still be free to withdraw from the study at any time, without having to give a reason.

Test subject's initials:.....

Date:.....

If you decide you would like to participate, initial each page of this form and sign the last page in the presence of the ICR staff. The Principal Investigator will sign the form as well, and you will be given a copy with both signatures. We will notify you by phone within one week whether you have been selected for the study.

**Eligibility for the Study**

To participate in this study you must meet the following conditions:

- Sex: Six of each: Male and Female
- Age: You must be at least 18 and not over 70
- Race: No exclusions
- Literacy: You must be able to read, speak, and understand English
- You must not be pregnant or breastfeeding. If you are female, you will be required to perform an over-the-counter urine pregnancy test on the morning of the study. ICR will provide the test kit, and a female ICR staff member will verify the results. ICR will keep the results of the pregnancy test confidential from everyone except you and the Principal Investigator.
- You must not be an employee or a relative of an employee of ICR Inc., LANXESS Corporation, or any other party with an interest in this research.
- You must have no known sensitivity to insect bites/stings, repellents or to skin care products

If you choose to participate in this study and are selected to be a study subject, you must also agree:

- To follow the directions of the Principal Investigator and other ICR staff..
- Not to use tobacco, alcohol, or any scented cosmetic products after 8 p.m. the night before study, and on the day of the study until it is concluded.

Test subject's initials:.....

Date:.....

**Dose Determination Phase Summary**

Twelve subjects will participate in this one-day laboratory study. Each of you will apply the cream repellent and the spray repellent to your arms three times. You will apply as much as you normally would, without any instructions from us as to how much to apply. We will measure the amount of repellent you applied and average that amount with the amount the other participants applied to determine the dose to be used in the repellent study. This study will take less than 9 hours for all 12 test subjects. If you finish early, you will be allowed to leave earlier. The entire test will be conducted in a room maintained at comfortable temperature and humidity.

**Procedures**

On the day of the study, before the test begins:

- We will review this document with you and answer any additional questions you may have since you have signed it.
- You will wash your arms with unscented Neutrogena® soap.
- We will measure and mark a 3 to 5 inch wide test area around each of your forearms as described in detail below.
- You will apply the spray and cream repellents three times to the treated area of your forearms in the amount that you would normally apply.
- We will weigh the amount of repellents you and the other 11 test subjects applied and average them to determine a testing dose.

**Here is how that will work in detail**

**Laboratory Study Details**

1. All 12 of you will be involved in treating your forearms with each of the two repellent products. You must not observe or discuss with other subjects any of these procedures.

Test subject's initials:.....

Date:.....

2. We will measure the distance around your arm at the wrist and the elbow, and calculate how wide a band is needed for the standard test area on your arm. This 3 - 5 inch wide band will be wider on thinner arms; narrower on bigger arms. We will then use a felt-tip pen to mark the location of the band around each of your forearms.

3. We will cover the skin above and below the marked test area with multiple layers of elastic bandages and or Velcro® straps held in place with adhesive tape.

4. You will then put on a latex or vinyl glove and use a gloved finger to apply the cream repellent to the treatment area of your forearm until you feel you have applied the amount of repellent you would apply if you were applying it at home.

5. We will determine how much product you applied by weighing the repellent container before and after you use it.

6. You will apply the cream repellent a total of three times in the same way. Between applications you will wash your forearm with unscented Neutrogena soap until you feel that you have washed off all the repellent. You will then dry your arm with a paper towel and then let it air dry until your arm feels completely dry.

7. We will then measure the amount of the spray repellent you would typically apply. We will take an average of your three applications and of all the other subjects. Finally we will take an average of these 12 subject averages.

8. We will wrap a 2 inch wide strip of waterproof dressing around the middle of the test area on your arm (waterproof side against your skin). Then we will wrap a 2 inch wide band of surgical gauze around the dressing. We will secure the gauze and the dressing with two rubber bands. Your forearm will now have a band of dressing (with gauze on top) and bare skin on either side.

9. You will then spray the second repellent over the entire marked out treatment band area of your forearm (including the gauze-covered dressing) until the amount of product you have applied to the two bare skin areas of your forearm feels like what you would apply if you were using the product at home.

Test subject's initials:.....

Date:.....

10. We will remove the gauze-covered dressing and weigh it to calculate the amount of product you applied.

11. You will repeat this spraying process two more times, washing and drying your forearm as you did with the cream repellent between applications. We will use new bands of dressing and gauze for each of the three sprayings.

12. Once you have applied both the cream and repellents three times, your involvement in the test is done. You may remove your bandages, wash your forearms, and go home.

13. The day's study may last up to nine hours for all 12 test subjects, although your direct involvement should not last more than three hours. You may either bring your own lunch or pay to have lunch ordered.

**Discomfort and Hazard**

**Reaction to the test repellents:**

You may have a reaction to the test repellents.

The Sponsor has minimized this possibility by choosing an active ingredient (picaridin) that has demonstrated low oral, skin, and inhalation toxicity. The Environmental Protection Agency (EPA) has classified it as low toxicity for inhalation toxicity and primary skin irritation. EPA has classified the two test repellents as having low to mild toxicity based on eye irritation. For this reason it is important not to rub your eyes with your treated arms. The Sponsor has selected the non-repellent ingredients in the formulations because they are widely used in cosmetics and have a long history of safe use. ICR staff will be monitoring all subjects for any signs of a reaction to the test repellents. If you think you may be having such a reaction, tell a member of the staff immediately. A reaction may include redness, irritation, burning, swelling or a rash.

Should you have any medical problems, we will have First- Aid- qualified staff members, and supplies on site. We will have cell phones to make emergency calls if necessary. In the case of medical emergency, we will transport you to a selected local hospital at our expense. We will pay all of your medical bills for study-related illnesses and injuries. The Principal Investigator will

Test subject's initials:.....

Date:.....

contact you by telephone, two weeks after the study to ask if you have experienced any adverse effects. You should contact the Principal Investigator any time after the study if you experience any study-related adverse effects, either before or after this follow up call.

**Financial Consideration**

We will pay you $11/hour for the 9 hour duration of the study for a total payment of $99. This payment will be mailed to you on the 15th or the last day of the month. If we ask you to drop out of the test, and you have complied with all of our requests, you will still receive full payment. If we ask you to drop out of the test because you have not followed all of our directions, or if you choose to drop out of the test, we will compensate you for time up to that point at the rate of $11 per hour.

**Costs**

There are no financial costs to you for participating in this study.

**Benefits**

You will get no personal benefit from participating in this study. The main benefit of this dose determination study is that it establishes the dose of the repellents to be tested in the subsequent stable fly repellent study.

Some benefit may result for society in general through showing the effectiveness of these products in repelling a noxious pest.

**Your Rights**

We will give you an opportunity to discuss with us any aspects of this document or of the study it describes that are not clear to you, so that you fully understand the nature of the study, its purpose, and the procedures to be used, as well as the discomforts, and risks you may experience during or after the study. You are encouraged to ask questions at any time, before or after you consent to participate, and before, during, or after the study day itself. Your participation is entirely voluntary. You may decide not to take part in this study, and if you decide you would like to participate, you

Test subject's initials:.....

Date:.....

are free to change your mind at any time without having to explain, and without penalty or loss of benefits to which you may be otherwise entitled.

**Alternative**

The only alternative is not to participate.

**New Information**

You will be informed verbally or in writing of any significant new findings discovered during the course of this study which may influence your continued participation.

**Voluntary Participation/Withdrawal**

You may be withdrawn from the study even if you want to continue. This could happen if (1) the study director believes it is in your best interest for you to stop being in the study, (2) or if you do not follow instructions for the study, (3) or if the sponsor stops the study for administrative or any other reasons.

**Questions**

If you have any questions about this study or suffer a reaction you think might be associated with the study, call us at 410-747-4500. If you have any questions about your rights as a research participant, or any related concerns or complaints, you may contact the Essex Institutional Review Board (IRB), 121 Main Street, Lebanon, NJ 08833, telephone 908-236-7735. The Essex IRB is a committee that has reviewed this research project to help ensure that the rights and welfare of the participants are protected and that the study is designed and carried out ethically. Review of this study by the Essex IRB is not an endorsement of the study or its outcome.

**Research Participation Information**

You can obtain information about participating in research studies from a number of sources.
A few are:

- Center for Information and Study on Clinical Research Participation (CISCRP): www.ciscrp.org
- Food and Drug Administration (FDA): www.fda.gov

Test subject's initials:.....

Date:.....

- Office for Human Research Protections (OHRP): www.hhs.gov/ohrp
- National Institute of Health: www.clinicaltrials.gov
- National Cancer Institute: www.nci.nih.gov
- Center Watch: www.centerwatch.com
- Various large university websites
- Various associations and societies concerned with specific diseases websites.

**Confidentiality**

We and the sponsor or its agents may use the information obtained from your taking part in this test, and this information may become part of a report. We will keep your participation as confidential as possible referring to you in the study data and reports only by your initials or an arbitrary ICR identification. However, we cannot guarantee that your identity will be kept confidential; the sponsor, personnel associated with the study, a regulatory agency such as the Environmental Protection Agency (EPA), and the Essex Institutional Review Board (EIRB) all have a right to review your records.

**Consent**

I voluntarily agree to participate in this study. I will be given a copy of this signed form.
By signing this form I have not given up any of my legal rights.

_____
Printed Name of Subject

_____
Signature of Subject Date

_____
Signature of Person Obtaining Consent Date

_____
Signature of Principal Investigator Date

Test subject's initials:.....

Date:.....

## APPENDIX III:
## INFORMED CONSENT DOCUMENT – REPELLENT TEST

Test subject's initials:.....

Date:.....

**PROTOCOL:** EVALUATION OF THE EFFICACY OF KBR 3023 (PICARIDIN; ICARIDIN) – BASED PERSONAL INSECT REPELLENTS (20% CREAM, 20% SPRAY) AGAINST STABLE FLIES IN THE LABORATORY

## INFORMED CONSENT AUTHORIZATION TO PARTICIPATE IN AN ICR, INC. STABLE FLY REPELLENT EVALUATION IN THE LABORATORY

**Principal Investigator: William J. Gaynor**
**Address: ICR, Inc. 1330 Dillon Heights Ave. Baltimore, MD**
**Telephone Number: 410-747-4500**
**24 Hour Emergency Number: 410-207-0415**

**Purpose of Study**

We (ICR, Inc.) have been contracted by LANXESS Corporation to conduct a research study in our laboratory on two insect repellent products containing the active ingredient picaridin, to find out how well these products repel stable flies. The stable flies used in this study are laboratory-reared and do not carry any diseases. This study will take place in the ICR, Inc. lab with stable flies confined in cages. This document will explain the study to you so that you can make a free choice whether or not to participate.

We will review this document with you to make sure you understand what would be expected of you if you participate, and to explain the risks you would face through your participation. Please ask us about anything you do not understand. If you have
have come into our office to review the document, you may take it home with you if you need more time to think about whether to participate.

We will apply the eligibility standard listed on the next page to determine if you qualify to participate in the study. If you qualify, we will ask you to consider signing this document to indicate your consent to participate. Your signing indicates your willingness to participate in this study, but you would still be free to withdraw from the study at any time, without having to give a reason.

Test subject's initials:.....

Date:.....

If you decide you would like to participate, initial each page of this form and sign the last page in the presence of the ICR staff. The Principal Investigator will sign the form as well, and you will be given a copy with both signatures. We will notify you by phone within one week whether you have been selected for the study.

**Eligibility for the Study**

To participate in this study you must meet the following conditions:

- Sex: Six of each: Male and Female (plus one extra of either sex)
- Age: You must be at least 18 and not over 70
- Race: No exclusions
- Literacy: You must be able to read, speak, and understand English
- You must be attractive to stable flies, as evidenced by at least 2 landings of caged stable flies on your untreated forearm within one minute.
- You must not be pregnant or breastfeeding. If you are female, you will be required to perform an over-the-counter urine pregnancy test on the morning of the study. ICR will provide the test kit, and a female ICR staff member will verify the results. ICR will keep the results of the pregnancy test confidential from everyone except you and the Principal Investigator.
- You must not be an employee or a relative of an employee of ICR Inc., LANXESS Corporation, or any other party with an interest in this research.
- You must have no known sensitivity to stable fly bites, to insect repellents, or to skin care products

If you choose to participate in this study and are selected to be a study subject, you must also agree

- To follow the directions of the Principal Investigator and other ICR staff.
- Not to use tobacco, alcohol, or any scented cosmetic products after 8 p.m. the night before the study, and on the day of the study until it is concluded.
- To wear proper protective clothing on the day of the study: blue jeans or other sturdy

Test subject's initials:.....

Date:.....

trousers, heavy socks, long sleeve shirts, and gloves. Gloves will be provided by ICR. The heavy clothing will help protect you from any stable flies which escape from the cages during testing.

**Laboratory Repellent Phase Summary**

Thirteen subjects will participate in this one-day laboratory study over a period of about 11 hours. One of you will be selected by chance (like pulling a number out of a hat) to serve as the "control subject", and will not be treated with the test repellents. The other 12 subjects will be "treated subjects", and will be treated with both of the repellents, one on each forearm. The entire test will be conducted in a room maintained at comfortable temperature and humidity.

Every 30 minutes during the test, the untreated control subject will put one untreated forearm into each test cage containing 25 stable flies for one minute. If fewer than 2 stable flies land within one minute, the stable flies will be vacuumed from all 6 test cages and 25 more stable flies will be added to each cage to ensure enough activity for a valid test.

After the untreated control subject has verified adequate stable fly activity, the 12 treated subjects will carefully put both forearms into their assigned cage with the stable flies for five minutes.

This pattern will be continued every half hour until you receive either two stable fly bites on the same arm in the same 5-minute exposure period, or one bite in each of two consecutive 5-minute exposure periods, or until ten hours after your treatment, whichever happens first.

**Procedures**

On the day of the study, before the test begins:

- We will review this document with you and answer any additional questions you may have since you have signed it.
- You will wash your arms with unscented Neutrogena®® soap.
- We will measure and mark a 3 to 5 inch wide test area around each of your forearms as described in detail below.

Test subject's initials:.....

Date:.....

- After we have measured your arms and protected the skin outside the test area, we will determine your attractiveness to stable flies as described below.

- Unless you are selected as the untreated control subject, we will treat both your arms with test repellents and the study will begin.

**Here is how that will work in detail**

**Laboratory Study Details**

1. One of you will be selected by chance (like pulling a number out of a hat) to be the untreated control subject.

2. We will measure the distance around your arm at the wrist and the elbow, and calculate how wide a band is needed for the standard test area on your arm. This 3 - 5 inch wide band will be wider on thinner arms; narrower on bigger arms. We will then use a felt-tip pen to mark the location of the band around each of your forearms. The control subject will be measured and marked on only one forearm.

3. We will protect the skin above and below the marked test area from stable fly bites with multiple layers of elastic bandages and or Velcro® straps held in place with adhesive tape.

4. We will verify that you are attractive to stable flies. You will put one forearm into a test cage containing 25 stable flies, and we will count the number of stable flies landing on your arm. We will brush landing stable flies off your arm before they have a chance to bite you. If 2 stable flies land on your arm in a minute or less you will qualify as "attractive". You will then repeat the same procedure with your other arm. If you are not attractive after one attempt, you may repeat the process a second time. If you fail to attract stable flies in two trials you may not be eligible to participate in the study.

5. If you are a treated subject, we will apply one of the repellents to the test area on each of your forearms, using a syringe without the needle. The amount of repellent applied will be a standardized "typical consumer dose". This amount will always be less than a quarter of a teaspoonful. If you are the untreated control subject, you will receive no treatment.

Test subject's initials:.....

Date:.....

6. With a fingertip in a latex or vinyl glove, we will spread the repellent evenly over the test areas. Once your arms have been treated, you must be careful not to rub them against anything, as this could rub off some of the test repellent and change the results of the study.

7. We will mark your bandages with a letter identifying the repellent applied to that arm. We will not identify the repellents to you.

8. You will go to the test laboratory and wait for your repellents to dry for about one-half hour. Then you will put on gloves to protect your hands from bites, ready for your first 5-minute exposure period of the day.

9. ICR staff will show you which cage to use. Treated subjects will work in pairs. If you see a stable fly land on your own or your partner's arm, notify ICR staff.

10. Every 30 minutes after the test begins, the untreated control subject will put one arm into each of the six test cages in turn, to verify stable fly activity. As soon as 2 stable flies land, the control subject will remove his or her arm from the cage. If fewer than 2 stable flies land on the control subject's arm within one minute, all of the flies in each of the 6 test cages will be vacuumed out and replaced with 25 fresh stable flies. ICR staff will brush away any landing stable flies from the control subject before the flies have time to bite. Nonetheless, it is likely that the control subject will get some bites during the course of the study.

11. Every 30 minutes after the study begins, after the activity of the stable flies in their assigned cage has been verified, each pair of treated subjects will carefully put both their arms into the cage for 5 minutes. During the 5-minute exposure period we will count the number of stable flies (up to two) that bite the treated skin of either of your arms. When you receive two bites on the same arm in one exposure period, or one bite in each of two consecutive exposure periods, you will remove that arm from the cage and from the study. We will call this "breakdown", and once you reach breakdown on one of your arms you will no longer expose that arm for the rest of the day's study. You can then remove the bandages and tape from this arm, and scratch if you choose. Caladryl®, Calamine® lotion and rubbing alcohol will be

Test subject's initials:.....

Date:.....

provided to help stop any itching from bites you received. When you reach breakdown on both arms, you will have finished your part in the study and may go home.

12. After each 5-minute exposure period you may leave the test room, but you must remain in the lab. You can go to the restroom if you need to, and the Study Director will call breaks every few hours. You may either bring your own lunch or pay to have lunch ordered.

13. After preparation and treatment of subjects, which will take about one hour, the day's study will include up to twenty 5-minute exposure periods at 30 minute intervals over 10 hours. The study will end after 10 hours or when all treated test subjects have reached breakdown on both arms, whichever comes first.

**Discomfort and Hazard**

**Stable fly bites**

A bite occurs when a stable fly lands and sticks its pointed mouthparts into your skin and takes blood. A stable fly bite will cause momentary pain and leave a small red mark which will usually disappear within a couple of days. The pain from a stable fly bites usually stops as soon as it stops biting. The irritation and swelling, which often result from mosquito bites, are not nearly so common after stable fly bites. In severe cases, a bite or probe may cause the development of large bumps on your skin, difficulty breathing, sweating and/or a rapid pulse. For some people this could be life-threatening.

All subjects will be exposed to stable flies for at least 1 minute to verify attractiveness to stable flies. Although we will try to brush the stable flies off before they bite, there is a slight possibility of being bitten. Treated subjects will expose their forearms to stable flies for five minutes every half hour. Although they will not expose an arm further if they receive two bites on it in one exposure, or one bite in two consecutive exposure periods, they may receive more than two bites on each arm during the test. A bite which is not followed by another bite in the same or the next exposure will be disregarded. If you are a treated subject you will still need to receive at least two more bites on that arm to reach breakdown. The untreated control subject will be exposed to stable flies every half hour for up to one minute in each of six test cages. Although we will try to

brush the landing stable flies off before they bite, the control subject is likely to be bitten by some of them. We will minimize the irritation from bites or probes you receive by making Caladryl® or Calamine® lotion or rubbing alcohol available at the study site for your use after the study is completed.

**Reaction to the test repellents**

You may have a reaction to the test repellents.

The Sponsor has minimized this possibility by choosing an active ingredient (picaridin) that has demonstrated low oral, skin, and inhalation toxicity. The Environmental Protection Agency (EPA) has classified it as low toxicity for acute inhalation toxicity and primary skin irritation. EPA has classified the two test repellents as having low to mild toxicity based on eye irritation. For this reason it is important not to rub your eyes with your treated arms. The Sponsor has selected the non-repellent ingredients in the formulations because they are widely used in cosmetics and have a long history of safe use. ICR staff will be monitoring all subjects for any signs of a reaction to the test repellents. If you think you may be having such a reaction, tell a member of the staff immediately. A reaction may include redness, irritation, burning, swelling or a rash.

The stable flies being used in this study will be laboratory-reared and disease-free, and they will never have had a human blood meal. There is therefore no risk of your contracting any stable fly-borne disease as a result of participation in this study.

Should you have any medical problems, we will have First- Aid- qualified staff members, and supplies on site. We will have cell phones to make emergency calls if necessary. In the case of medical emergency, we will transport you to a selected local hospital at our expense. We will pay all of your medical bills for study-related illnesses and injuries. The Principal Investigator will contact you by telephone, two weeks after the study to ask if you have experienced any adverse effects. You should contact the Principal Investigator any time after the study if you experience any study-related adverse effects, either before or after this follow up call.

**Financial Consideration**

We will pay you $11/hour for the first 9 hours and $17.50 for each additional hour that you spend on the day of the study. The study will last about 10 hours with an additional hour of prep time (11

Test subject's initials:.....

Date:.....

hours total), with a total payment of $134. This payment will be mailed to you on the 15th or the last day of the month. If we ask you to drop out of the test, and you have complied with all of our requests, you will still receive full payment. If we ask you to drop out of the test because you have not followed all of our directions, or if you choose to drop out of the test, we will compensate you for time up to that point at the rate of $11 per hour.

**Costs**

There are no financial costs to you for participating in this study.

**Benefits**

You will get no personal benefit from participating in this study.
Some benefit may result for society in general through showing the effectiveness of these products in repelling a noxious pest.

**Your Rights**

We will give you an opportunity to discuss with us any aspects of this document or of the study it describes that are not clear to you, so that you fully understand the nature of the study, its purpose, and the procedures to be used, as well as the discomforts, and risks you may experience during or after the study. You are encouraged to ask questions at any time, before or after you consent to participate, and before, during, or after the study day itself. Your participation is entirely voluntary. You may decide not to take part in this study, and if you decide you would like to participate, you are free to change your mind at any time without having to explain, and without penalty or loss of benefits to which you may be otherwise entitled.

**Alternative**

The only alternative is not to participate.

**New Information**

You will be informed verbally or in writing of any significant new findings discovered during the course of this study which may influence your continued participation.

Test subject's initials:.....

Date:.....

**Voluntary Participation/Withdrawal**

You may be withdrawn from the study even if you want to continue. This could happen if (1) the study director believes it is in your best interest for you to stop being in the study, (2) or if you do not follow instructions for the study, (3) or if the sponsor stops the study for administrative or any other reasons.

**Questions**

If you have any questions about this study or suffer a reaction you think might be associated with the study, call us at 410-747-4500. If you have any questions about your rights as a research participant, or related concerns, you may contact the Essex Institutional Review Board (IRB), 121 Main Street, Lebanon, NJ 08833, telephone 908-236-7735. The Essex IRB is a committee that has reviewed this research project to help ensure that the rights and welfare of the participants are protected and that the study is designed and carried out ethically. Review of this study by the Essex IRB is not an endorsement of the study or its outcome.

**Research Participation Information**

You can obtain information about participating in research studies from a number of sources.
A few are:

- Center of Information and Study on Clinical Research Participation (CISCRP): www.ciscrp.org
- Food and Drug Administration (FDA): www.fda.gov
- Office for Human Research Protections (OHRP): www.hhs.gov/ohrp
- National Institute of Health: www.clinicaltrials.gov
- National Cancer Institute: www.nei.nih.gov
- Center Watch: www.centerwatch.com
- Various large university websites
- Various associations and societies concerned with specific diseases websites.

Test subject's initials:.....

Date:.....

**Confidentiality**

We and the sponsor or its agents may use the information obtained from your taking part in this test, and this information may become part of a report. We will keep your participation as confidential as possible referring to you in the study data and reports only by your initials or an arbitrary ICR identification. However, we cannot guarantee that your identity will be kept confidential; the sponsor, personnel associated with the study, a regulatory agency such as the Environmental Protection Agency (EPA), and the Essex Institutional Review Board (EIRB) all have a right to review your records.

**Consent**

I voluntarily agree to participate in this study. I will be given a copy of this signed form.
By signing this form I have not given up any of my legal rights.

_____

Printed Name of Subject

_____

Signature of Subject Date

_____

Signature of Person Obtaining Consent Date

_____

Signature of Principal Investigator Date

Test subject's initials:.....

Date:.....

## APPENDIX IV:
## LABELS FOR PRODUCTS

Test subject's initials:.....

Date:.....

# KBR 3023 Insect Repellent Cream

**Contains Bayrepel™. Long-lasting, effective protection from mosquitoes ticks, biting flies, gnats, chiggers, sand 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**

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

LANXESS

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

### 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.

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

LABEL TEXT DATE:

ACCEPTED
with COMMENTS
In EPA Letter Dated
APR 10 2007
Under the Federal Insecticide, Fungicide, and Rodenticide Act, as amended, for the pesticide Registered under EPA Reg. No. 39967-50

# KBR 3023 All-Family Insect Repellent Spray

**Long-lasting, effective protection from mosquitoes, ticks, biting flies, gnats, chiggers, sand flies, 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.:**

ACCEPTED
APR 16 2007
Under the Federal Insecticide, Fungicide, and Rodenticide Act, as amended, for the pesticide Registered under EPA Reg. No. 39967-53

LANXESS

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

LABEL TEXT DATE:

## APPENDIX V:
## PRODUCT TOXICOLOGY

Test subject's initials:.....

Date:.....

**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 I4-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 $_{a2u}$ globulin accumulation. The toxicology profile by oral route of exposure did not reveal any new targets compared to the dermal route and. 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/200rng/kg/day- the highest dose tested).

Test subject's initials:.....

Date:.....

**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

## APPENDIX VI: RECRUITMENT SCRIPT

Repellent Test Recruitment Telephone Script
Protocol Number: G4330108001A382
Protocol Version Date: February 1, 2008
Subject Initials/#:

**ICR will be conducting a stable fly repellent study and a dose determination study for the this main repellent study on these dates, (Month, Day(s), Year). The location of these studies will be the ICR laboratory at 1330 Dillon Heights Avenue, Catonsville, Maryland. Will you be available on these dates?**

***If the person is available the inclusion/exclusion criteria will be discussed to verify whether the person qualifies to participate.***

**I will now read the inclusion criteria to you to see if you qualify to participate in the study.**

Inclusion Criteria:
**Please let me know if you do not satisfy any of the following inclusion criteria:**

**We will accept an equal number of male and female participants.**
**You must be between 18 and 70 years old.**
**There are no race restrictions.**
**You must be able to read, speak, and understand English.**
**You must consider yourself to be in good health.**
**For the repellent study only, you must be attractive to stable flies. We must verify this in the lab by inserting your untreated forearm into a cage of stable flies to see if at least 2 stable flies land within one minute.**

**I will now read the exclusion criteria to you to see if you do not qualify to participate in the study.**

Exclusion Criteria:
**Please let me know if you can satisfy the following exclusion criteria:**

**You cannot participate if you are pregnant or breastfeeding. All female subjects will be required to perform a urine OTC pregnancy test on the morning of the study.**

**You cannot participate if you are an employee or a relative of an employee of ICR Inc., the sponsor, toXcel, LLC, or any interested party.**

**For the repellency test only, you cannot participate if you are sensitive to stable fly bites.**

**You cannot participate if you have any known sensitivity to insect repellents or skin care products.**

*If an individual elects to participate in the study, after they have satisfied the inclusion/exclusion criteria, they must agree to the following:*

**I will now read a list of items that you must agree to in order to participate in the study. You must agree to follow the directions of the Principal Investigator and other ICR staff.**

**You must agree to abstain from the use of tobacco, alcohol, and all scented cosmetic products after 8 p.m. the night before the study, and on the day of the study until it is concluded.**

**For the repellent study only, you must agree to wear proper protective clothing such as blue jeans, heavy socks, long sleeve shirt, and gloves (gloves provided by ICR).**

*If an individual elects to participate in the study, after they have satisfied the inclusion/exclusion criteria and agree to follow the above we will then discuss the test with them.*

STABLE FLY REPELLENT STUDY

**You will be one of thirteen subjects who participate in this one-day laboratory study lasting about 11 hours. One of you will be selected by chance to serve as the "control subject", and will not be treated with the test repellents. The other 12 of you will be "treated subjects", and will be treated with both of the repellents, one on each forearm.**

**Every 30 minutes during the test, the untreated control subject will put one untreated forearm into each test cage containing 25 stable flies for one minute. If fewer than 2 stable flies land within one minute, these stable flies will be vacuumed from the cage and 25 more stable flies will be added to each cage to ensure enough activity for a valid test.**

**After the untreated control subject has verified adequate mosquito activity, the 12 treated subjects will carefully put both forearms into their assigned cage with the stable flies for five minutes.**

**This pattern will be continued every half hour until you receive either two stable fly bites on the same arm in the same 5-minute exposure period, or one bite in each of two consecutive 5-minute exposure periods, or until ten hours after your treatment, whichever happens first.**

DOSE DETERMINATION STUDY

**You will be one of twelve subjects who will participate in this one-day laboratory study**

**lasting probably less than 4 hours. Each of you will apply the two test repellents (a cream and a spray) three times to a marked out area of your forearm. We will measure the amount of repellent you and the other eleven subjects apply and average these amounts to determine how much repellent will be applied in the subsequent repellent study.**

***If an individual is still interested in participating in either study, we will discuss the ICD with them.***

**You are being asked to participate in a research study. Before agreeing to participate in this study, it is important that you read a form. This form is called an informed consent document. The informed consent document describes the purpose, procedures, benefits, financial payment, risks and discomforts of the study. It also describes the alternative procedures that are available to you and your right not to participate or to withdraw from the study at anytime. Please ask as many questions as you need to so that you can decide whether you want to be in the study. After reading this and having all questions answered, if you decide to participate, you should return this consent form to the to the study director. Sign the last page, initial and date each prior page in the presence of the study staff. You may refuse to participate in this study and this decision will not be held against you. If you are still interested in participating in the study we will mail an informed consent document to you for your review. In addition, after you have read the informed consent document, we would like you to come to the ICR office in person so that we can discuss the informed consent document with you and answer any questions that you may have. However if you are not able to visit our office prior to the study date, you must subsequently sign the ICD on the morning of the study at the ICR laboratory if you still wish to participate in the study.**

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**PROTOCOL:** EVALUATION OF THE EFFICACY OF KBR 3023 (PICARIDIN; ICARIDIN) – BASED PERSONAL INSECT REPELLENTS (20% CREAM, 20% SPRAY) AGAINST STABLE FLIES IN THE LABORATORY

## INFORMED CONSENT AUTHORIZATION TO PARTICIPATE IN THE DOSE DETERMINATION PHASE OF AN ICR, INC. STABLE FLY REPELLENT EVALUATION IN THE LABORATORY

**Principal Investigator: William J. Gaynor**
**Address: ICR, Inc. 1330 Dillon Heights Ave. Baltimore, MD**
**Telephone Number: 410-747-4500**
**24 Hour Emergency Number: 410-207-0415**

### Purpose of Study

We (ICR, Inc.) have been contracted by LANXESS Corporation to conduct a research study in our laboratory on two insect repellent products containing the active ingredient picaridin, to find out how well these products repel stable flies. Before this study can be performed the dose of the two repellents to be used in the study must be determined based on how much product a typical consumer would apply to themselves. This dose determination phase of the study is the study for which we are asking you for your participation. This dose determination phase of the study will occur in the ICR, Inc. lab where the stable fly repellents will later be tested using the doses you determine today. We have prepared this Informed Consent Document (ICD) to explain this dose determination study to you so that you can make a free choice whether or not to participate.

We will review this document with you to make sure you understand what would be expected of you if you participate, and to explain the risks you would face through your participation. Please ask us about anything you do not understand. If you have have come into our office to review the document, you may take it home with you if you need more time to think about whether to participate.

Test subject's initials:.....

Date:.....

We will apply the eligibility standard listed below to determine if you qualify to participate in the study. If you qualify, we will ask you to consider signing this document to indicate your consent to participate. Your signing indicates your willingness to participate in this study, but you would still be free to withdraw from the study at any time, without having to give a reason.

If you decide you would like to participate, initial each page of this form and sign the last page in the presence of the ICR staff. The Principal Investigator will sign the form as well, and you will be given a copy with both signatures. We will notify you by phone within one week whether you have been selected for the study.

**Eligibility for the Study**

To participate in this study you must meet the following conditions:

- Sex: Six of each: Male and Female
- Age: You must be at least 18 and not over 70
- Race: No exclusions
- Literacy: You must be able to read, speak, and understand English
- You must not be pregnant or breastfeeding. If you are female, you will be required to perform an over-the-counter urine pregnancy test on the morning of the study. ICR will provide the test kit, and a female ICR staff member will verify the results. ICR will keep the results of the pregnancy test confidential from everyone except you and the Principal Investigator.
- You must not be an employee or a relative of an employee of ICR Inc., LANXESS Corporation, or any other party with an interest in this research.
- You must have no known sensitivity to insect bites/stings, repellents or to skin care products

If you choose to participate in this study and are selected to be a study subject, you must also agree:

Test subject's initials:.....

Date:.....

- To follow the directions of the Principal Investigator and other ICR staff.

- Not to use tobacco, alcohol, or any scented cosmetic products after 8 p.m. the night before study, and on the day of the study until it is concluded.

**Dose Determination Phase Summary**

Twelve subjects will participate in this one-day laboratory study. Each of you will apply the cream repellent and the spray repellent to your arms three times. You will apply as much as you normally would, without any instructions from us as to how much to apply. We will measure the amount of repellent you applied and average that amount with the amount the other participants applied to determine the dose to be used in the repellent study. This study will take less than 9 hours for all 12 test subjects. If you finish early, you will be allowed to leave earlier. The entire test will be conducted in a room maintained at comfortable temperature and humidity.

**Procedures**

On the day of the study, before the test begins:

- We will review this document with you and answer any additional questions you may have since you have signed it.

- You will wash your arms with unscented Neutrogena® soap.

- We will measure and mark a 3 to 5 inch wide test area around each of your forearms as described in detail below.

- You will apply the spray and cream repellents three times to the treated area of your forearms in the amount that you would normally apply.

- We will weigh the amount of repellents you and the other 11 test subjects applied and average them to determine a testing dose.

Test subject's initials:.....

Date:.....

**Here is how that will work in detail**

**Laboratory Study Details**

1. All 12 of you will be involved in treating your forearms with each of the two repellent products. You must not observe or discuss with other subjects any of these procedures.

2. We will measure the distance around your arm at the wrist and the elbow, and calculate how wide a band is needed for the standard test area on your arm. This 3 - 5 inch wide band will be wider on thinner arms; narrower on bigger arms. We will then use a felt-tip pen to mark the location of the band around each of your forearms.

3. We will cover the skin above and below the marked test area with multiple layers of elastic bandages and or Velcro® straps held in place with adhesive tape.

4. You will then put on a latex or vinyl glove and use a gloved finger to apply the cream repellent to the treatment area of your forearm until you feel you have applied the amount of repellent you would apply if you were applying it at home.

5. We will determine how much product you applied by weighing the repellent container before and after you use it.

6. You will apply the cream repellent a total of three times in the same way. Between applications you will wash your forearm with unscented Neutrogena soap until you feel that you have washed off all the repellent. You will then dry your arm with a paper towel and then let it air dry until your arm feels completely dry.

7. We will then measure the amount of the spray repellent you would typically apply. We will take an average of your three applications and of all the other subjects. Finally we will take an average of these 12 subject averages.

Test subject's initials:.....

Date:.....

8. We will wrap a 2 inch wide strip of waterproof dressing around the middle of the test area on your arm (waterproof side against your skin). Then we will wrap a 2 inch wide band of surgical gauze around the dressing. We will secure the gauze and the dressing with two rubber bands. Your forearm will now have a band of dressing (with gauze on top) and bare skin on either side.

9. You will then spray the second repellent over the entire marked out treatment band area of your forearm (including the gauze-covered dressing) until the amount of product you have applied to the two bare skin areas of your forearm feels like what you would apply if you were using the product at home.

10. We will remove the gauze-covered dressing and weigh it to calculate the amount of product you applied.

11. You will repeat this spraying process two more times, washing and drying your forearm as you did with the cream repellent between applications. We will use new bands of dressing and gauze for each of the three sprayings.

12. Once you have applied both the cream and repellents three times, your involvement in the test is done. You may remove your bandages, wash your forearms, and go home.

13. The day's study may last up to nine hours for all 12 test subjects, although your direct involvement should not last more than three hours. You may either bring your own lunch or pay to have lunch ordered.

Test subject's initials:.....

Date:.....

**Discomfort and Hazard**

**Reaction to the test repellents:**

You may have a reaction to the test repellents.

The Sponsor has minimized this possibility by choosing an active ingredient (picaridin) that has demonstrated low oral, skin, and inhalation toxicity. The Environmental Protection Agency (EPA) has classified it as low toxicity for inhalation toxicity and primary skin irritation. EPA has classified the two test repellents as having low to mild toxicity based on eye irritation. For this reason it is important not to rub your eyes with your treated arms. The Sponsor has selected the non-repellent ingredients in the formulations because they are widely used in cosmetics and have a long history of safe use. ICR staff will be monitoring all subjects for any signs of a reaction to the test repellents. If you think you may be having such a reaction, tell a member of the staff immediately. A reaction may include redness, irritation, burning, swelling or a rash.

Should you have any medical problems, we will have First- Aid- qualified staff members and supplies on site. We will have cell phones to make emergency calls if necessary. In the case of medical emergency, we will transport you to a selected local hospital at our expense. We will pay all of your medical bills for study-related illnesses and injuries. The Principal Investigator will contact you by telephone, two weeks after the study to ask if you have experienced any adverse effects. You should contact the Principal Investigator any time after the study if you experience any study-related adverse effects, either before or after this follow up call.

**Financial Consideration**

We will pay you $11/hour for the 9-hour duration of the study for a total payment of $99. This payment will be mailed to you on the 15th or the last day of the month. If we ask you to drop out of the test, and you have complied with all of our requests, you will still receive full payment. If we ask you to drop out of the test because you have not followed all of our directions, or if you choose to drop out of the test, we will compensate you for time up to that point at the rate of $11 per hour.

Test subject's initials:.....

Date:.....

**Costs**

There are no financial costs to you for participating in this study.

**Benefits**

You will get no personal benefit from participating in this study. The main benefit of this dose determination study is that it establishes the dose of the repellents to be tested in the subsequent stable fly repellent study. Some benefit mayresult for society in general through showing the effectiveness of these products in repelling a noxiouspest.

**Your Rights**

We will give you an opportunity to discuss with us any aspects of this document or of the study it describes that are not clear to you, so that you fully understand the nature of the study, its purpose, and the procedures to be used, as well as the discomforts, and risks you may experience during or after the study. You are encouraged to ask questions at any time, before or after you consent to participate, and before, during, or after the study day itself. Your participation is entirely voluntary. You may decide not to take part in this study, and if you decide you would like to participate, you are free to change your mind at any time without having to explain, and without penalty or loss of benefits to which you may be otherwise entitled.

**Alternative**

The only alternative is not to participate.

**New Information**

You will be informed verbally or in writing of any significant new findings discovered during the course of this study which may influence your continued participation.

Test subject's initials:.....

Date:.....

**Voluntary Participation/Withdrawal**

You may be withdrawn from the study even if you want to continue. This could happen if (1) the study director believes it is in your best interest for you to stop being in the study, (2) or if you do not follow instructions for the study, (3) or if the sponsor stops the study for administrative or any other reasons.

**Questions**

If you have any questions about this study or suffer a reaction you think might be associated with the study, call us at 410-747-4500. If you have any questions about your rights as a research participant, or any related concerns or complaints, you may contact the Essex Institutional Review Board (IRB), 121 Main Street, Lebanon, NJ 08833, telephone 908-236-7735. The Essex IRB is a committee that has reviewed this research project to help ensure that the rights and welfare of the participants are protected and that the study is designed and carried out ethically. Review of this study by the Essex IRB is not an endorsement of the study or its outcome.

Research Participation Information

You can obtain information about participating in research studies from a number of sources.
A few are:

- Center for Information and Study on Clinical Research Participation (CISCRP); www.ciscrp.org
- Food and Drug Administration (FDA): www.fda.gov
- Office for Human Research Protections (OHRP): www.hhs.gov/ohrp
- National Institute of Health: www.clinicaltrials.gov
- National Cancer Institute: www.nci.nih.gov
- Center Watch: www.centerwatch.com
- Various large university websites
- Various associations and societies concerned with specific diseases websites.

Test subject's initials:.....

Date:.....

**Confidentiality**

We and the sponsor or its agents may use the information obtained from your taking part in this test, and this information may become part of a report. We will keep your participation as confidential as possible referring to you in the study data and reports only by your initials or an arbitrary ICR identification. However, we cannot guarantee that your identity will be kept confidential; the sponsor, personnel associated with the study, a regulatory agency such as the Environmental Protection Agency (EPA), and the Essex Institutional Review Board (EIRB) all have a right to review your records.

**Consent**

I voluntarily agree to participate in this study. I will be given a copy of this signed form. By signing this form I have not given up any of my legal rights.

_____
Printed Name of Subject

_____
Signature of Subject Date

_____
Signature of Person Obtaining Consent Date

_____
Signature of Principal Investigator Date

Test subject's initials:.....

Date:.....

**PROTOCOL:** EVALUATION OF THE EFFICACY OF KBR 3023 (PICARIDIN; ICARIDIN) – BASED PERSONAL INSECT REPELLENTS (20% CREAM, 20% SPRAY) AGAINST STABLE FLIES IN THE LABORATORY

## INFORMED CONSENT AUTHORIZATION TO PARTICIPATE IN AN ICR, INC. STABLE FLY REPELLENT EVALUATION IN THE LABORATORY

**Principal Investigator: William J. Gaynor**
**Address: ICR, Inc. 1330 Dillon Heights Ave. Baltimore, MD**
**Telephone Number: 410-747-4500**
**24 Hour Emergency Number: 410-207-0415**

### Purpose of Study

We (ICR, Inc.) have been contracted by LANXESS Corporation to conduct a research study in our laboratory on two insect repellent products containing the active ingredient picaridin, to find out how well these products repel stable flies. The stable flies used in this study are laboratory-reared and do not carry any diseases. This study will take place in the ICR, Inc. lab with stable flies confined in cages. This document will explain the study to you so that you can make a free choice whether or not to participate.

We will review this document with you to make sure you understand what would be expected of you if you participate, and to explain the risks you would face through your participation. Please ask us about anything you do not understand. If you have have come into our office to review the document, you may take it home with you if you need more time to think about whether to participate.

We will apply the eligibility standard listed on the next page to determine if you qualify to participate in the study. If you qualify, we will ask you to consider signing this document to indicate your consent to participate. Your signing indicates your willingness to participate in this study, but you would still be free to withdraw from the study at any time, without having to give a reason.

Test subject's initials:.....

Date:.....

If you decide you would like to participate, initial each page of this form and sign the last page in the presence of the ICR staff. The Principal Investigator will sign the form as well, and you will be given a copy with both signatures. We will notify you by phone within one week whether you have been selected for the study.

**Eligibility for the Study**

To participate in this study you must meet the following conditions:

- Sex: Six of each: Male and Female (plus one extra of either sex)
- Age: You must be at least 18 and not over 70
- Race: No exclusions
- Literacy: You must be able to read, speak, and understand English
- You must be attractive to stable flies, as evidenced by at least 2 landings of caged stable flies on your untreated forearm within one minute.
- You must not be pregnant or breastfeeding. If you are female, you will be required to perform an over-the-counter urine pregnancy test on the morning of the study. ICR will provide the test kit, and a female ICR staff member will verify the results. ICR will keep the results of the pregnancy test confidential from everyone except you and the Principal Investigator.
- You must not be an employee or a relative of an employee of ICR Inc., LANXESS Corporation, or any other party with an interest in this research.
- You must have no known sensitivity to stable fly bites, to insect repellents, or to skin care products.
- If you choose to participate in this study and are selected to be a study subject, you must also agree:
- To follow the directions of the Principal Investigator and other ICR staff.
- Not to use tobacco, alcohol, or any scented cosmetic products after 8 p.m.

Test subject's initials:.....

Date:.....

the night before study, and on the day of the study until it is concluded.

- To wear proper protective clothing on the day of the study: blue jeans or other sturdy trousers, heavy socks, long sleeve shirts, and gloves. Gloves will be provided by ICR. The heavy clothing will help protect you from any stable flies which escape from the cages during testing.

**Laboratory Repellent Phase Summary**

Thirteen subjects will participate in this one-day laboratory study over a period of about 11 hours. One of you will be selected by chance (like pulling a number out of a hat) to serve as the "control subject", and will not be treated with the test repellents. The other 12 subjects will be "treated subjects", and will be treated with both of the repellents, one on each forearm. The entire test will be conducted in a room maintained at comfortable temperature and humidity.

Every 30 minutes during the test, the untreated control subject will put one untreated forearm into each test cage containing 25 stable flies for one minute. If fewer than 2 stable flies land within one minute, the stable flies will be vacuumed from all 6 test cages and 25 more stable flies will be added to each cage to ensure enough activity for a valid test.

After the untreated control subject has verified adequate stable fly activity, the 12 treated subjects will carefully put both forearms into their assigned cage with the stable flies for five minutes.

This pattern will be continued every half hour until you receive either two stable fly bites on the same arm in the same 5-minute exposure period, or one bite in each of two consecutive 5-minute exposure periods, or until ten hours after your treatment, whichever happens first.

**Procedures**

On the day of the study, before the test begins:

- We will review this document with you and answer any additional questions you

may have since you have signed it.

- You will wash your arms with unscented Neutrogena® soap.
- We will measure and mark a 3 to 5 inch wide test area around each of your forearms as described in detail below.
- After we have measured your arms and protected the skin outside the test area, we will determine your attractiveness to stable flies as described below.
- Unless you are selected as the untreated control subject, we will treat both your arms with test repellents and the study will begin.

**Here is how that will work in detail**

**Laboratory Study Details**

1. One of you will be selected by chance (like pulling a number out of a hat) to be the untreated control subject.

2. We will measure the distance around your arm at the wrist and the elbow, and calculate how wide a band is needed for the standard test area on your arm. This 3 - 5 inch wide band will be wider on thinner arms; narrower on bigger arms. We will then use a felt-tip pen to mark the location of the band around each of your forearms. The control subject will be measured and marked on only one forearm.
3. We will protect the skin above and below the marked test area from stable fly bites with multiple layers of elastic bandages and or Velcro® straps held in place with adhesive tape.

4. We will verify that you are attractive to stable flies. You will put one forearm into a test cage containing 25 stable flies, and we will count the number of stable flies landing on your arm. We will brush landing stable flies off your arm before they have a chance to bite you. If 2 stable flies land on your arm in a minute or less you will qualify as "attractive". You will then repeat the same

breathing, sweating and/or a rapid pulse. For some people this could be life-threatening.

All subjects will be exposed to stable flies for at least 1 minute to verify attractiveness to stable flies. Although we will try to brush the stable flies off before they bite, there is a slight possibility of being bitten.

Treated subjects will expose their forearms to stable flies for five minutes every half hour. Although they will not expose an arm further if they receive two bites on it in one exposure, or one bite in two consecutive exposure periods, they may receive more than two bites on each arm during the test. A bite which is not followed by another bite in the same or the next exposure will be disregarded. If you are a treated subject you will still need to receive at least two more bites on that arm to reach breakdown. The untreated control subject will be exposed to stable flies every half hour for up to one minute in each of six test cages. Although we will try to brush the landing stable flies off before they bite, the control subject is likely to be bitten by some of them. We will minimize the irritation from bites or probes you receive by making Caladryl® or Calamine® lotion or rubbing alcohol available at the study site for your use after the study is completed.

**Reaction to the test repellents**

You may have a reaction to the test repellents.

The Sponsor has minimized this possibility by choosing an active ingredient (picaridin) that has demonstrated low oral, skin, and inhalation toxicity. The Environmental Protection Agency (EPA) has classified it as low toxicity for inhalation toxicity and primary skin irritation. EPA has classified the two test repellents as having low to mild toxicity based on eye irritation. For this reason it is important not to rub your eyes with your treated arms. The Sponsor has selected the non-repellent ingredients in the formulations because they are widely used in cosmetics and have a long history of safe use. ICR staff will be monitoring all subjects for any signs of a reaction to the test repellents. If you think you may be having such a reaction, tell a member of the staff immediately. A reaction may include redness, irritation, burning, swelling or a rash.

The stable flies being used in this study will be laboratory-reared and disease-free, and

Test subject's initials:.....

Date:.....

they will never have had a human blood meal. There is therefore no risk of your contracting any stable fly-borne disease as a result of participation in this study.

Should you have any medical problems, we will have First- Aid- qualified staff members and supplies on site. We will have cell phones to make emergency calls if necessary. In the case of medical emergency, we will transport you to a selected local hospital at our expense. We will pay all of your medical bills for study-related illnesses and injuries. The Principal Investigator will contact you by telephone, two weeks after the study to ask if you have experienced any adverse effects. You should contact the Principal Investigator any time after the study if you experience any study-related adverse effects, either before or after this follow up call.

**Financial Consideration**

We will pay you $11/hour for the first 9 hours and $17.50 for each additional hour that you spend on the day of the study. The study will last about 10 hours with an additional hour of prep time (11 hours total), with a total payment of $134. This payment will be mailed to you on the 15$^{th}$ or the last day of the month. If we ask you to drop out of the test, and you have complied with all of our requests, you will still receive full payment. If we ask you to drop out of the test because you have not followed all of our directions, or if you choose to drop out of the test, we will compensate you for time up to that point at the rate of $11 per hour.

**Costs**

There are no financial costs to you for participating in this study.

**Benefits**

You will get no personal benefit from participating in this study.
Some benefit mayresult for society in general through showing the effectiveness of these products in repelling a noxious pest.

Test subject's initials:.....

Date:.....

**Your Rights**

We will give you an opportunity to discuss with us any aspects of this document or of the study it describes that are not clear to you, so that you fully understand the nature of the study, its purpose, and the procedures to be used, as well as the discomforts, and risks you may experience during or after the study. You are encouraged to ask questions at any time, before or after you consent to participate, and before, during, or after the study day itself. Your participation is entirely voluntary. You may decide not to take part in this study, and if you decide you would like to participate, you are free to change your mind at any time without having to explain, and without penalty or loss of benefits to which you may be otherwise entitled.

**Alternative**

The only alternative is not to participate.

**New Information**

You will be informed verbally or in writing of any significant new findings discovered during the course of this study which may influence your continured participation.

**Voluntary Participation/Withdrawal**

You may be withdrawn from the study even if you want to continue. This could happen if (1) the study director believes it is in your best interest for you to stop being in the study, (2) or if you do not follow instructions for the study, (3) or if the sponsor stops the study for administrative or any other reasons.

**Questions**

If you have any questions about this study or suffer a reaction you think might be associated with the study, call us at 410-747-4500. If you have any questions about

Test subject's initials:.....

Date:.....

your rights as a research participant, or any related concerns or complaints, you may contact the Essex Institutional Review Board (IRB), 121 Main Street, Lebanon, NJ 08833, telephone 908-236-7735. The Essex IRB is a committee that has reviewed this research project to help ensure that the rights and welfare of the participants are protected and that the study is designed and carried out ethically. Review of this study by the Essex IRB is not an endorsement of the study or its outcome.

**Research Participation Information**

You can obtain information about participating in research studies from a number of sources.

A few are:

- Center for Information and Study on Clinical Research Participation (CISCRP): www.ciscrp.org
- Food and Drug Administration (FDA): www.fda.gov
- Office for Human Research Protections (OHRP)" www.hhs.gov/ohrp
- National Institute of Health: www.clinicaltrials.gov
- National Cancer Institute: www.nei.nih.gov
- Center Watch: www.centerwatch.com
- Various large university websites
- Various associations and societies concerned with specific diseases websites.

**Confidentiality**

We and the sponsor or its agents may use the information obtained from your taking part in this test, and this information may become part of a report. We will keep your participation as confidential as possible referring to you in the study data and reports only by your initials or an arbitrary ICR identification. However, we cannot guarantee that your identity will be kept confidential; the sponsor, personnel associated with the study, a regulatory agency such as the Environmental Protection Agency (EPA), and the Essex Institutional Review Board (EIRB) all have a right to review your records.

Test subject's initials:.....

Date:.....

**Consent**

I voluntarily agree to participate in this study. I will be given a copy of this signed form. By signing this form I have not given up any of my legal rights.

_____
Printed Name of Subject

_____
Signature of Subject Date

_____
Signature of Person Obtaining Consent Date

_____
Signature of Principal Investigator Date

Test subject's initials:.....

Date:.....

# ESSEX IRB

## INVESTIGATOR CONFLICT OF INTEREST DECLARATION

Study title and number: "Evaluation of the Efficacy of KBR 3023 (Picaridin: Icaridin) - Based Personal Insect Repellents (20% Cream and 20% Spray) Against Stable Flies in the Laboratory". ICR Project Number: 0108-433-0161; Protocol Number: G4330108001A382 WJG 2/5/08

Sponsor: LANXESS Corporation

Financial relationships of investigators (or institutions/sites) to sponsors have the potential to adversely affect the rights and welfare of human subjects involved in research. In order to help ensure that such issues do not compromise the results or create hazards for the subjects, Essex IRB requests you to make a declaration regarding any conflict of interest (COI) in the conduct or outcome of the trial. To achieve this, we ask you to answer the following questions and submit a response to any that have a "Yes" reply in a separate letter.

- Do you have any relationship with the sponsor or institution that could cause potential or actual conflict of interest? Yes ☐ No ☒
  If yes, describe the degree of conflict and with which parties.
- Is there any compensation that your institutional ethics/COI committee has deemed to be a conflict or could affect the outcome of the trial?
  Yes ☐ No ☒ If yes, describe.
- Does anyone involved with the research have proprietary interests in the product, drug or device, including patents, trademarks, copyright and licensing agreements? Yes ☐ No ☒ If yes, describe.
- Does anyone have an equity interest in the research sponsor?
  Yes ☐ No ☒ Describe, if yes.
- Do you receive significant payments, equipment, retainers, incentives, grants or honoraria from the sponsor? Yes ☐ No ☒ If yes, describe.
- Are the payments or incentives you receive per participant considered to be outside the norm? Yes ☐ No ☒ If yes, describe.

You may submit a letter from your institution's COI Committee regarding their determination of any COI in this study. Any recommendations you or they make to reduce or eliminate any COI will be appreciated. Examples of these are: describing any COI in the informed consent form, having an impartial third party obtain consent, reduction or elimination of the financial interest or equity ($50000 or greater), monitoring by an impartial party (independent data and safety committee), or separation of duties or roles (e.g., change of principal investigator). Violation of this declaration may result in it being reported to the FDA or OHRP (Office for Human Research Protection), as well as, our terminating approval for you to conduct this research study.

We thank you for indulgence in completing this document. If you have any questions, please contact us.

Principal Investigator's Printed Name: William J. Gaynor

Signature: William J Gaynor Date: 1/23/2008

procedure with your other arm. If you are not attractive after one attempt, you may repeat the process a second time. If you fail to attract stable flies in two trials you may not be eligible to participate in the study.

5. If you are a treated subject, we will apply one of the repellents to the test area on each of your forearms, using a syringe without the needle. The amount of repellent applied will be a standardized "typical consumer dose". This amount will always be less than a quarter of a teaspoonful. If you are the untreated control subject, you will receive no treatment.

6. With a fingertip in a latex or vinyl glove, we will spread the repellent evenly over the test areas. Once your arms have been treated, you must be careful not to rub them against anything, as this could rub off some of the test repellent and change the results of the study.

7. We will mark your bandages with a letter identifying the repellent applied to that arm. We will not identify the repellents to you.

8. You will go to the test laboratory and wait for your repellents to dry for about one-half hour. Then you will put on gloves to protect your hands from bites, ready for your first 5-minute exposure period of the day.

9. ICR staff will show you which cage to use. Treated subjects will work in pairs. If you see a stable fly land on your own or your partner's arm, notify ICR staff.

10. Every 30 minutes after the test begins, the untreated control subject will put one arm into each of the six test cages in turn, to verify stable fly activity. As soon as 2 stable flies land, the control subject will remove his or her arm from the cage. If fewer than 2 stable flies land on the control subject's arm within one minute, all of the flies in each of the 6 test cages will be vacuumed out and replaced with 25 fresh stable flies. ICR staff will brush away any landing stable flies from the control subject before the flies have time to bite. Nonetheless, it is likely that the control subject will get some bites during the course of the study.

Test subject's initials:.....

Date:.....

11. Every 30 minutes after the study begins, after the activity of the stable flies in their assigned cage has been verified, each pair of treated subjects will carefully put both their arms into the cage for 5 minutes. During the 5-minute exposure period we will count the number of stable flies (up to two) that bite the treated skin of either of your arms. When you receive two bites on the same arm in one exposure period, or one bite in each of two consecutive exposure periods, you will remove that arm from the cage and from the study. We will call this "breakdown", and once you reach breakdown on one of your arms you will no longer expose that arm for the rest of the day's study. You can then remove the bandages and tape from this arm, and scratch if you choose. Caladryl®, Calamine® lotion and rubbing alcohol will be provided to help stop any itching from bites you received. When you reach breakdown on both arms, you will have finished your part in the study and may go home.

12. After each 5-minute exposure period you may leave the test room, but you must remain in the lab. You can go to the restroom if you need to, and the Study Director will call breaks every few hours. You may either bring your own lunch or pay to have lunch ordered.

13. After preparation and treatment of subjects, which will take about one hour, the day's study will include up to twenty 5-minute exposure periods at 30 minute intervals over 10 hours. The study will end after 10 hours or when all treated test subjects have reached breakdown on both arms, whichever comes first.

**Discomfort and Hazard**

**Stable fly bites**

A bite occurs when a stable fly lands and sticks its pointed mouthparts into your skin and takes blood. A stable fly bite will cause momentary pain and leave a small red mark which will usually disappear within a couple of days. The pain from a stable fly bites usually stops as soon as it stops biting. The irritation and swelling, which often result from mosquito bites, are not nearly so common after stable fly bites. In severe cases, a bite or probe may cause the development of large bumps on your skin, difficulty