UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

MEMORANDUM:

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

May 24, 2007

SUBJECT: Science and Ethics Review of Protocol for Human Study of Mosquito Repellent Performance

FROM: John M. Carley
Human Research Ethics Review Officer

Kevin Sweeney,
Science Reviewer

TO: Marion Johnson, Chief
Insecticide Branch, RD

REF: Spero, N. (2007) Protocol for Conducting Insect Repellent Field Efficacy Testing on Mosquitoes Including Supporting Materials Satisfying 40 CFR §26.1125 for Test Materials 1003715-019 & 1003715-020. Document dated April 11, 2007. Unpublished document prepared by Insect Control & Research, Inc., under Protocol ID G0590307001A044. 161 p.

We have reviewed the referenced protocol for a field test of mosquito repellency from both scientific and ethics perspectives. This review assesses the scientific aspects of the proposed research in terms of the recommendations of the draft EPA Guidelines 810.3700 and of the EPA Human Studies Review Board, and the ethical aspects of the proposed research in terms of the standards defined by 40 CFR 26 subparts K and L and the recommendations of the EPA Human Studies Review Board.

A. Completeness of Protocol Submission

The submitted protocol was reviewed for completeness against the required elements listed in 40 CFR §26.1125. EPA's checklist is appended to this review as Attachment 5. The following elements of required documentation were not provided in the submitted protocol package:

- A discussion of the balance of risks and benefits of the proposed research, as required by 40 CFR §26.1125(a)(5)
- Minutes of IRB meetings in sufficient detail to show the basis for requiring changes in the protocol and Informed Consent documents, as required by §26.1115(a)(2)
- Written procedures for the IRB in the same detail as described in §26.1108(a) and §26.1108(b).

None of these omissions is significant enough to prevent a meaningful review of the proposed research. Although the rule requires that the IRB procedures be submitted, and although the investigators report (p. 7B)[1] only that they are available for inspection at the EIRB site in New Jersey, the complete procedures manual for Essex IRB was previously submitted directly to EPA.

In addition to the protocol itself (pp. 11-41) the submitted package included the following supporting documents—all considered in this review:

- Initial transmittal of protocol to EIRB (p. 9)
- Informed Consent Documents (ICs)
  - As initially submitted to the EIRB (pp. 42-66)
  - As revised 4/5/07 and resubmitted to the EIRB (pp. 112-127)
  - As approved by EIRB 4/9/07 (pp. 138-154)
- Site Application Letter to EIRB
  - As initially submitted to the EIRB (pp. 67-78)
  - As revised in response to EIRB requests (pp. 129-135)
- MSDSs for test materials (pp. 79-84)
- Curriculae vitae of Principal and other Investigators (pp. 85-95)
- Indemnification Agreements
  - Sponsor/ICR (p. 96)
  - Sponsor/EIRB (p. 158)
- "Investigator Attestation of Qualifications" (p. 97)
- "Investigator Conflict of Interest Declaration" (p. 98)
- EIRB report of conditional approval 4/3/07 (pp. 99-103)
- Minutes of EIRB meeting of 4/2/07 (pp. 104-108)
- Transmittal of revisions to EIRB 4/5/07 (p. 109)
- Promise by ICR to make changes in protocol requested by EIRB (pp. 110-111)
- E-mail report from EIRB to ICR of 4/6/07 approval of protocol amendments and revised ICs, and requesting additional clarifications in Site Application Letter and an additional c.v. (p. 128)
- EIRB approval letter of 4/9/07 (pp. 136-137)
- List of Members of EIRB (pp. 155-157)
- EIRB "Statement of Compliance" (p. 159)
- EIRB Brochure (pp. 160-161)

[1] Many sections of the submission are paginated more than once; all page references in this review are to the "n of 161" page number.

B. Summary Assessment of Ethical Aspects of the Proposed Research

Here is a summary of the ethical aspects of the proposed protocol. Supporting details are in Attachment 1.

1. **Societal Value of Proposed Research:** The stated purpose of the proposed research is to evaluate the efficacy of two topical picaridin-based repellents against mosquitoes in two field locations for up to 12 hours. EPA requires product-specific field efficacy data to support registration of repellents; these test materials have not previously been tested in the field.

2. **Subject Selection:** Subjects will be recruited from a database including previous subjects of similar ICR tests and "friends and colleagues" of previous subjects. This pool is characterized as being "as representative of potential repellent users as we are able to make it." Explicit factors exclude as subjects children, adults over 65, pregnant or nursing women, non-English speakers and those in poor health. The sample will thus not be fully representative of the population of potential repellent users. Two subjects selected by lot will serve as untreated controls each test day to verify ambient biting pressure from mosquitoes in the field.

   It is generally accepted that vulnerability to West Nile Virus is greater for those over about 50 or 55. Including subjects over 55 in a test of repellency of mosquitoes which could vector WNV is not consistent with risk minimization for those subjects.

   There is no clear indication that any subjects will be from populations potentially vulnerable to coercion or undue influence. But inconsistencies among multiple statements of eligibility factors suggest that some employees of ICR might be recruited as subjects—i.e., those who work part-time, or who work full-time on an other-than-permanent basis—as well as employees of the sponsor. These inconsistencies are not acknowledged, and neither justification for including employees as subjects nor specific safeguards to protect their rights and welfare are discussed.

   Overall remuneration of subjects would be $676.50, plus air travel to and from the test area, plus all expenses of lodging and meals for six days. That may be high enough to serve as a considerable inducement to participate. Since, however, subjects are recruited mainly from among previous subjects of similar tests, it is unlikely that this would unduly influence someone to participate against his/her better judgment.

3. **Risks to Subjects:** Risks of three kinds are discussed: the risk of reaction to the repellents tested, the risk of reaction to arthropod bites, and the risk of contraction of an arthropod-borne disease.

- The discussion in the Informed Consent Document of risks of reaction to the repellents tested is misleading in at least two respects, and should be changed to address more directly the risks associated with the test materials themselves.

    - First, while EPA may have assigned technical picaridin to Toxicity Category IV for acute inhalation toxicity and skin irritation, these are not the pathways of greatest toxicity for picaridin, and the material to which subjects may react is not picaridin per se, but the formulated test materials. The incomplete MSDSs provided for the test materials indicate by inclusion of the signal word "Warning" that categorization is expected in Toxicity Category II based on eye irritancy and possibly other properties. While acute toxicity data reporting on testing of the two formulations proposed for testing in this research have not been submitted, EPA has classified other generally similar formulations of picaridin in Toxicity Category III for eye irritation (requiring the signal word "Caution") and in Toxicity Category IV for other routes of acute exposure. The signal word required on the label is always based on the lowest-numbered Toxicity Category for any route of acute exposure.

    - Second, the suggestion that the formulations including inert ingredients are "beneficial for skin care and safe for direct human exposure" is unsupported and an unacceptable safety claim.

  Risks of reaction to the repellents are reduced by excluding candidates with a history of allergic reactions to repellents or skin care products and by monitoring subjects closely for reactions.

  At the proposed dose rate each treated subject will receive some 833 mg repellent applied to 500 cm^2 skin. The concentration of picaridin in the test materials is not greater than the 20% previously registered by EPA in other products; assuming 20% picaridin as the worst case, 833 mg product is equivalent to 167 mg picaridin. Because of the ethanol in the formulations this figure is adjusted by an "ethanol enhancement" factor of 2.26, yielding an adjusted dose of 377 mg, or 5.4 mg/kg for a 70 kg adult. The NOAEL for acute dermal toxicity in the rat for picaridin is 5000 mg/kg bodyweight, picaridin is less readily absorbed by human skin than by rat skin, and we do not expect the inert ingredients other than ethanol to affect the systemic dermal toxicity. Thus the estimated margin of exposure for picaridin dermal toxicity is not less than—and may be substantially greater than—5000/5.4 or 926.

- The discussion of risks of arthropod bites addresses steps taken to minimize the risks but not the risks themselves. Risks of arthropod bites are reduced by excluding candidates with a history of severe reactions to mosquito bites, by

intermittent exposure of only a small area of treated skin, by covering treated skin between exposure periods and immediately after efficacy breakdown, by moving away from mosquito-infested areas between exposure periods, by teaming treated subjects in pairs to watch each other for landing mosquitoes, by minimizing the number of untreated control subjects, by exposing untreated controls only long enough to confirm continued mosquito landing pressure, by brushing away mosquitoes attempting to bite with fewer than all six of their legs on the treated area of skin, and by treating subject (and staff) shoes with permethrin to repel ticks. Further reduction in risks of mosquito bites is possible by treating landings as evidence not only of biting pressure but of efficacy failure as well, and by more thoughtful attention to stopping rules.

- Conflicting statements are made about the risk of arthropod-borne diseases. The protocol states: "Since the EPA requires demonstration of the repellency of mosquitoes known to carry specific diseases such as the WNV in order to substantiate related product claims, the sponsor is compelled to conduct field testing in areas in which test subjects will attract these potential vector species." In marked contrast the Informed Consent Document informs potential subjects "The disease risks you will be exposed to are primarily from the bites of mosquitoes. Fortunately, most of these diseases do not occur naturally in the United States, but diseases like malaria and dengue are occasionally introduced by travelers. Mosquitoes are also known to carry various types of encephalitis viruses such as West Nile Virus (WNV). The principal carriers of the WNV are not common at the test site." These conflicting statements must be reconciled. Risks of arthropod-borne disease are reduced by the same actions taken to reduce bites, and by conducting field tests in areas where West Nile virus has not been detected by the local Mosquito Abatement District for at least a week. These risks could be further reduced with an improved medical management plan and provision for post-exposure follow-up, and by excluding subjects over 55 years old.

Additional risk-reduction measures include availability of first aid materials and first-aid qualified staff, notifying a local hospital of the study before it is conducted, and carrying cell-phones for emergency calls.

4. **Benefits:** The protocol states that participating in the research will "probably" be of no benefit to subjects; the word "probably" in this context should be deleted. The protocol also acknowledges that the research will benefit the sponsor, who can expect it to support a future application for pesticide registration. The protocol does not discuss the societal benefit of the knowledge likely to be gained other than to assert that more and different repellent products available to consumers represents a societal benefit, and that the data to be developed in the proposed research is essential to satisfy regulatory requirements for bringing new repellents to market. In summary, if the testing shows good field efficacy the direct beneficiary of the research is likely to be the sponsor. Assuming eventual

regulatory approval, indirect beneficiaries would include those repellent users who prefer the new formulations to previously available repellents.

5. **Risk/Benefit Balance:** The protocol reduces but does not minimize the risks to subjects. In particular, risks of both irritation and disease from mosquito bites could be further reduced by treating landings as evidence of a failure of efficacy, rather than only bites. The exclusion as evidences of efficacy failure of landings, probes, and bites with fewer than all six legs of a biting mosquito on the treated skin serves not to make the study more "realistic from a public health perspective"—as is asserted in the protocol—but to make it both riskier for the subjects and a less demanding test of product performance. Additional opportunities to further reduce risks to subjects include an improved medical management plan, more thoughtful attention to stopping rules, and provision for post-exposure follow-up.

   There are no direct benefits of this research to the subjects, so justification depends on the anticipated benefits to society from the information likely to be gained. The protocol discussion of benefit does not address the benefits of the knowledge likely to be gained from the research, but instead asserts the benefit of bringing alternative repellents to market. Since these test materials fall within the ranges of picaridin concentration and product forms EPA has previously accepted for registration, they are likely to differ only slightly from others already in the market.

   Notwithstanding the weaknesses of the arguments concerning the expected benefit of this research, there is potential societal benefit in a wide range of differing effective repellent products, both from a public health perspective and from a nuisance-reduction perspective. If the risks to subjects are further reduced as suggested above, the residual risks are likely to be reasonable in light of the potential benefit to consumers of a wider range of choice in effective mosquito repellents.

5. **Independent Ethics Review:** The protocol has been reviewed and approved by Essex Institutional Review Board (EIRB) of Lebanon, NJ. EIRB is registered with OHRP, but does not hold an FWA. Although the protocol asserts that EIRB is accredited by PHRP, EIRB does not appear in the list of accredited organizations on the PHRP website (www.phrp.org). The protocol also asserts that EIRB "is in the process of obtaining accreditation from AAHRPP," but as of May 17, 2007, EIRB did not appear on the list of accredited organizations on the AAHRBB website (www.aahrpp.org). EIRB has not provided a copy of its procedures to either the investigators (ICR) or to EPA, as is required by 40 CFR 26.1125; this is a serious deficiency. Although minutes are provided of the EIRB meeting on April 2, 2007, at which this protocol was discussed, they do not explain the basis for requiring changes in the protocol and informed consent document. Since most required changes were minor editorial changes this is a less serious deficiency. The protocol as submitted includes a promise by ICR to

make numerous minor changes in the protocol directed by EIRB, but it does not include a revised protocol approved by the EIRB.

The discussion of ICR policies and their compliance with DHHS regulations and EPA's "model rule" on pp. 19-20 evidences confusion about the status and applicability of the EPA rules to the proposed research and, in suggesting that compliance with those rules requires ICR only to submit "a protocol, informed consent document, and standard indemnification forms to an independent institutional review board," about what those rules require.

6. **Informed Consent:** The protocol as submitted includes several preliminary versions of the Informed Consent (IC) documents as well as the final versions (one specific to the Georgia test site; the other to the Florida test site) approved by the EIRB. These IC documents satisfy the applicable requirements of 40 CFR 26.1116 and 26.1117.

Potential subjects are initially contacted by telephone from a database of former subjects of repellency tests. Those who are available to travel to the site of the planned research at the time it is planned, who are "interested" in participating, and who meet the eligibility criteria are provided a copy of the IC document, either in person (if the candidate lives in the Baltimore area and is willing to travel to the ICR laboratory) or by mail. Many of the potential subjects in the ICR database do not live near Baltimore, and distribution of the IC document by mail is likely to be the predominant method. After receipt of the IC document is confirmed, the P.I. discusses it with the candidate—typically by telephone—and answers any questions. The candidate then may choose to sign the IC document in front of a witness, who also signs it, and the signed IC is mailed to ICR. When the P.I. signs it as well, a copy is mailed back to the subject with travel information.

The process of informing candidates and seeking their consent is described in several places in the protocol and IC documents, all differing in important details. A single clear and authoritative description of the process is needed, and other references to it should be consistent.

8. **Respect for Subjects:** Methods proposed for managing information about prospective and enrolled subjects will generally protect their privacy from compromise. All data collection forms include spaces for both subject name and subject signature; it would provide greater assurance of privacy to identify subjects by code on all but one master directory that links names to codes.

"Females will be required to perform an over the counter pregnancy test . . . . on the morning of the test. The results will be verified by a qualified female ICR staff member. . . . The results of this pregnancy test will be kept confidential and will not be disclosed to anyone other than the test subject and the P.I.." (p. 30) Although recruitment of alternate subjects provides some opportunity for discrete

withdrawal without explanation, this may not provide adequately for the protection of the privacy of subjects who might be found to be pregnant only after traveling to the test area and participating in the evening-before-the-test activities.

Adequate provision is made in the proposed protocol for managing withdrawals from the research for other reasons. Medical care for research-related injuries will be provided at no cost to the subjects.

C. Compliance with Applicable Ethical Standards

This is a protocol for third-party research involving intentional exposure of human subjects to a pesticide, with the intention of submitting the resulting data to EPA under the pesticide laws. Thus the primary ethical standards applicable to this proposal are 40 CFR 26, Subparts K and L. In addition, the requirements of FIFRA §12(a)(2)(P) for fully informed, fully voluntary consent of subjects apply. Because the test will be conducted in California, the provisions of the California Code of Regulations, Title 3, §6710 apply as well. A point-by-point evaluation of how the requirements of 40 CFR 26 Subparts K and L and the criteria recommended by the HSRB are addressed is appended as Attachment 1.

The following specific deficiencies should be corrected before the research is initiated:

- Including subjects over 55 in a test of repellency of mosquitoes which could vector WNV is not consistent with risk minimization for those subjects. Either exclude subjects over 55 or justify their inclusion.

- Clarify exclusion factors concerning employees. Either exclude all employees of ICR or the sponsor or of any other entity with an interest in the research, or justify not excluding all of them and describe the specific safeguards in place. Safeguards must not only protect included subjects from coercion or undue influence, but must also protect the integrity of the research from any bias. Make all references to exclusion of employees consistent.

- Risks of mosquito bites could be further reduced by treating landings as evidence not only of biting pressure but of efficacy failure as well. The emphasis on distinguishing landings from probes, and probes from bites, and bites with six legs on treated skin from other bites, is not adequately explained or justified.

- Risks of contracting an arthropod-borne disease could be further reduced by including provision for post-exposure follow-up

The discussion of ICR policies and their compliance with DHHS regulations and EPA's "model rule" on pp. 19-20 should be replaced by a straightforward commitment that this research will be conducted in compliance with 40 CFR part 26, subparts K and L.

- The process of informing candidates and seeking their consent is described differently in several places in the protocol and Informed Consent documents. A single clear and authoritative description of the process is needed, and all references to it should be consistent.

- All data collection forms provide for recording both subject name and subject signature; it would provide greater protection of subject privacy to identify them by code on all but one master directory that links names to codes.

- Although recruitment of alternate subjects provides some opportunity for discrete withdrawal without explanation, this may not be adequate to protect the privacy of subjects who are found to be pregnant only after traveling to the test area and participating in the evening-before-the-test activities.

When these deficiencies have been corrected, the entire proposal must be re-reviewed and approved by the IRB before research can proceed or subjects can be enrolled.

40 CFR 26 Subpart L, at §26.1703, as amended effective August 22, 2006, provides in pertinent part:

> EPA shall not rely on data from any research involving intentional exposure of any human subject who is a pregnant woman (and therefore her fetus), a nursing woman, or a child.

The protocol requires that subjects be at least 18 years old and excludes female subjects who are pregnant or lactating. Thus §26.1703 would not forbid EPA to rely on a study executed according to this protocol.

D. Summary Assessment of Scientific Aspects of the Proposed Research

The study will test the field efficacy as a mosquito repellent of two unregistered repellent formulations containing picaridin (KBR 3023). The objective of the study is to quantify the efficacy of the formulations to prevent mosquito bites in the field.

Biting pressure will be monitored for five minutes every 30 minutes during the test by two untreated subjects. Mosquitoes landing on untreated subjects will be flicked away to prevent biting; some will be collected for later identification. Treated subjects will work in pairs to facilitate observations, and will expose treated skin for 5 minutes at 30 minute intervals until they experience a confirming bite or until the end of the test period—whichever comes first.

1. **Study design:** The objective of the study is to determine the field efficacy of two unregistered mosquito repellent aerosol spray formulations containing picaridin. The objectives of the study can be met as proposed and will result in (Complete) Protection Times for each formulations based on the mean time to First Confirmed Bite.

2. **Statistical design:** The sample size is greater than recommended by the EPA Testing Guidelines–large enough to ensure robust averages across subjects, but small enough to be economical. Two subjects will be used to establish ambient biting pressure at each test interval; no statistical comparisons to the untreated controls are proposed. Ten subjects will be treated with the test formulations. There will be an additional two control subjects, plus two additional treated test subjects to replace anyone that either drops out or is ineligible to participate due to a positive pregnancy test or other unforeseen circumstances. These additional two treated test subjects will help to ensure a minimum "n" of ten. No positive or negative control treatment will be evaluated concurrently or included in the test design. The test is subject-blinded. The test repellents will be coded as 'A' and 'B', and each arm will be labeled on the protective wrap with the code corresponding to the repellent applied. Repellency will be reported as Protection Time (PT) and will be expressed in whole hour units. The PT will be measured as the mean time from initial application of the test formulation to the First Confirmed Bite (FCB), and will be presented with a standard deviation of the mean and a 95% confidence interval. However, it is not clear what statistical procedures will be applied to analyze the data.

   If a test subject protection time appears to be an "outlier" (one that appears to deviate markedly from the other members of the sample in which it occurs), that data will be subjected to the test for outlying observations as described in ASTM E 178-94 'Standard Practice for Dealing with Outlying Observations'. If the subject is identified as an "outlier", the data collected on that subject will not be included in the statistical analysis. EPA believes that such data should not be excluded as an "outlier" observation, but should be included in the determination of mean Complete Protection Time.

3. **How and to what will human subjects be exposed?** The test formulations will be applied to the skin of each subject at the rate of 1g/600cm^2, equivalent to 1.67 mg/cm^2. This dose is pre-determined by the sponsor and is consistent with typical consumer doses for DEET-based repellents. A dosimetry study will not be performed. The repellent will remain in place for up to 12 hours.

4. **Endpoints and Measures:** The endpoint is Protection Time (PT) and will be expressed in whole hour units. PT will be measured as the mean time from initial application of the test formulation to the First Confirmed Bite (FCB), and will be presented with a standard deviation of the mean and a 95% confidence interval. A FCB is defined as the "a bite which is followed by another bite in either the same 5 minutes exposure period or the next consecutive 5 minutes exposure period". Subjects will be trained to recognize a bite and bites will be confirmed by the Study Director and ICR staff. For consistency with other repellent study data, EPA recommends that the endpoint be known as Complete Protection Time (CPT) rather than Protection Time (PT).

E. Compliance with applicable Scientific standards

This protocol adequately addresses the following elements according to applicable scientific standards:

- Scientific objectives
- Experimental design for achieving objectives
- Quantification of repellency of the test materials
- Data collection, compilation and summary of test results
- Justification for dose of each formulation applied to the subjects
- Justification for samples size in repellency phase.
- Rationale for use of two untreated subjects to monitor biting pressure

This protocol does not adequately address the following elements:

- No explicit hypothesis is stated
- Information on diagnostic testing for normality, or information on how to analyze non-normally distributed data is lacking.
- Justification for exclusion of "outlier" results is inadequate
- A reference to published GLP procedures in 40CFR Part 160 is needed in the discussion of Quality Assurance

Attachments:

1. Summary Review of ICR Protocol ICR G0590307001A044 dated 4/11/07
2. §26.1111 Criteria for IRB approval of research
3. §26.1116 General requirements for informed consent
4. §26.1117 Documentation of informed consent
5. §26.1125 Criteria for Completeness of Proposals for Human Research

EPA Protocol Review: ICR G0590307001A044

Title: Protocol for Conducting Insect Repellent Field Efficacy Testing on Mosquitoes Including Supporting Materials Satisfying 40 CFR §26.1125 for Test Materials 1003715-019 & 1003715-020. Unpublished document prepared by Insect Control & Research, Inc., under Protocol ID G0590307001A044.

Date: 11 April 2007

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1. Societal Value of Proposed Research

(a) What is the stated purpose of the proposed research?

"The objective is to evaluate the efficacy of two topical picaridin-based repellents against mosquitoes in two field locations. . . . This study will evaluate the efficacy of two picaridin-based repellents which have not been previously tested in the field for a duration of up to 12 hours." (p. 13)

(b) What research question does it address? Why is this question important? Would the research fill an important gap in understanding?

"Under FIFRA, EPA requires submission of such human efficacy study data . . . in support of insect repellent product registration. Each new repellent formulation must have performance studies conducted on human subjects to substantiate the product's label claims." (p. 13)

(c) How would the study be used by EPA?

EPA will consider the study in defining acceptable label claims for repellent efficacy for the test materials.

(d) Could the research question be answered with existing data? If so, how? If not, why not?

EPA requires product-specific efficacy data to support registration. The proposed test materials have not previously been field tested for efficacy.

(e) Could the question be answered without newly exposing human subjects? If so, how? If not, why not?

"According to the draft EPA OPPTS Guideline No. 810.3700 'Product Performance of Skin-Applied Repellents of Insect and Other Arthropods', there exists no alternative to evaluating topical repellents on human subjects in the field; therefore, field testing repellents is necessary." (p. 15)

"Human subjects are required for this study because they represent the feeding target of the mosquitoes. The purpose of these repellents is to prevent mosquitoes from biting humans. There are no satisfactory substitute models for testing repellency to mosquitoes. While there has been experimental work on product repellency accomplished using mice or guinea pigs, the data did not give reliable results when compared to data gathered from human subjects." (p. 19)

2. Study Design

(a) What is the scientific objective of the study? If there is an explicit hypothesis, what is it?

"The objective is to evaluate the efficacy of two topical picaridin-based repellents against mosquitoes in two field locations. . . . This study will evaluate the efficacy of two picaridin-based repellents which have not been previously tested in the field for a duration of up to 12 hours." (p. 13)

No explicit hypothesis is stated.

(b) Can the study as proposed achieve that objective or test this hypothesis?

The objective cited above can be achieved by the study as proposed.

2.1 Statistical Design

(a) What is the rationale for the choice of sample size?

"The EPA Guideline . . . recommends at least six test subjects be used. Because of the cost of doing field studies, it is prudent to ensure data collected will give a good representation of the repellency of the test formulations. In a published paper the number of subjects required to achieve an estimated among-subjects standard deviation for specific times of 0.5 hours to 2.0 hours was calculated for protection times from 1 hour to 8 hours. The number of subjects required to achieve an estimated among-subjects standard deviation of 2.0 hours at a 95% confidence level for an 8 hour protection time was calculated to be between 10 and 11 subjects. This study, therefore, will use ten treated test subjects. There will be an additional two control subjects, plus two additional treated test subjects to replace anyone that either drops out or is ineligible to participate due to a positive pregnancy test or other unforeseen circumstances. These additional two treated test subjects will help to ensure a minimum "n" of ten and will aid in protecting the privacy of any dropouts." (p. 27) The proposed sample size promises to provide an acceptably robust measure of average complete protection time at reasonable cost.

(b) What negative and positive controls are proposed? Are proposed controls appropriate for the study design and statistical analysis plan?

"Sufficient biting pressure . . . will be confirmed . . . throughout the study. One untreated arm of each of the two control subjects will serve as negative controls. These controls will be selected at random from the total pool of test subjects by drawing names. Different subjects will be used as controls for each day of the study. This will be accomplished by removing the names of subjects already used as negative controls from the pool when drawing names of subjects to be used for the next day's test. . . . Negative controls will be used to monitor the level of mosquito activity in the area by baring the 250 cm^2 untreated area on their arm for up to five minutes every one-half hour while the study director or an assistant counts the number of mosquitoes that land on the bare skin." (p. 21)

"A positive control is intentionally excluded . . . for several reasons. The sponsor understands that such practice is generally discouraged in these types of studies by the EPA/OPP and that positive controls in these types of studies are optional. Data on a positive control group serves no purpose in this study to confirm the mosquito repellency of the test product and determine a reliable protection period under real-

life field conditions. Putting additional subjects at risk, however minimal, to include a positive control group is not necessary." (p. 22)

Use of two untreated controls to confirm continued pest pressure throughout the field testing is appropriate for the study design. Omission of matrix and positive controls is acceptable for the study design. No direct comparisons of treated and untreated subjects are contemplated in the statistical analysis plan.

(d) How is the study blinded?

"This is a subject-blinded study. . . . The test samples will be coded as 'A' and 'B'. During the test these codes will be the only test sample designation referred to or that the test subjects will see. The Study Director and members of the ICR staff will know the actual test samples. . . ." (p. 29)

"The test repellents will be coded as 'A' and 'B', 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'." (p. 31)

(d) What is the plan for allocating individuals to treatment or control groups?

"There will be two groups for each test location: . . . a treated group of twelve subjects . . . , and an untreated (control) group of two test subjects. . . . They will be assigned to the groups by lottery selection. . . ." (p. 29)

"There will be twelve test arms for each treatment. Each test subject will have one arm treated with one of the two test products and the other arm will be treated with the other test product." (p. 29)

(e) Can the data be statistically analyzed?

Yes. The study provides for testing in two distinct locations. At each location from ten to twelve individual values for CPT will be obtained for each test material and averaged. At least some of the subjects are likely to be different in the two field tests.

(f) What is the plan for statistical analysis of the data?

"Efficacy data will be reported as Protection Time which is the mean hours and minutes to FCB or test termination. We will calculate the time of complete protection for the test repellents. Therefore, the time to first confirmed bite for all treated test subjects will be averaged and the standard deviation computed. A 95% confidence limit will be determined. If a test subject protection time appears to be an "outlier" (one that appears to deviate markedly from the other members of the sample in which it occurs), that data will be subjected to the test for outlying observations as described in ASTM E 178-94 'Standard Practice for Dealing with Outlying Observations'. If

the test indicates that the observation is an outlier, that data point will be discarded." (p. 34)

EPA recommends that these data be reported as part of the GLP study and that these observations be included in the analysis. It is feasible to view the possibility of "outliers" in a population but this is difficult to determine in a sample.

"If a test subject wishes to drop out of the study before the stated end point, the data from that test subject will not be used in calculating the mean PT of the test repellent. Any treated arms that do not breakdown within the twelve hour time frame of the study will be given a value of twelve for PT. All data will be entered into a CoStat program for the calculation of the standard deviation and the 95% confidence limit. (p. 34).

EPA recommends that data from drop-outs be included in the analysis of CPT if the subject has received bites during the field trial.

(g) Are proposed statistical methods appropriate to answer the research question?

The proposed statistical measure for duration of repellency is appropriate in the case that the data are normally distributed. The protocol does not address how to analyze non-normally distributed data. Based on efficacy data for other repellents, a distribution effectively close to a normal fit would be expected, but the protocol should incorporate a diagnostic test for normality, and discuss data transformation procedures or alternate non-parametric tests for statistical analyses of data which may not fit a normal distribution.

(h) Does the proposed design have adequate statistical power to definitively answer the research question?

Yes. It will produce a data set more robust than most on which past decisions by EPA concerning acceptable claims of repellency have been based.

2.2 How and to what will human subjects be exposed?

(a) What is the rationale for the choice of test material and formulation?

The test materials are two developmental formulations for which the sponsor intends to seek registration, each containing picaridin as the sole active ingredient. The proposed research to test their efficacy in the field is part of the development of data to support registration.

(b) What is the rationale for the choice of dose/exposure levels and the staging of dose administration?

The proposed research does not include any direct measurement of user self-dosing behavior. The appropriate "typical consumer dose" has been assumed to be equal to the accepted standard dose for lotion repellents containing Deet—i.e., 1 g/600 cm^2. This standard unit dose, adjusted for the use of a 250 cm^2 treatment area, and for the specific gravity of the test formulations, will be used for all subjects in the efficacy phase. Each arm of each treated subject will be treated with one of the two test repellents; exposure to the repellents will be continuous throughout the period of the test.

Subjects will also be exposed for five of every 30 minutes during the efficacy trial in Georgia to "natural adult populations of mosquitoes found in the Coastal area of Georgia . . . . primarily *Aedes vexans*, *Psorophora ferox*, and *Ochlerotatus infirmatus."* Subjects in the trial in Florida will be exposed for five of every 30 minutes during the study to "natural adult populations of mosquitoes found in the Gulf Coast area of Florida . . . . *Ochlerotatus taeniorhynchus* plus other minor occurrences of native species." (p. 19)

(c) What duration of exposure is proposed?

"The study duration could be 14 hours or more: preparing your arms for the test, along with preparing the other test subjects, will take about one hour; transport to and from the study site could take up to one hour; exposures to mosquitoes will go on for up to 12 hours." (IC p. 141, 150)

"The study itself will take one day, but we will allocate a total of six days for the trip to allow for travel time, foul weather and study-related time. If you are chosen to participate in this study, you will be paid for a total of six days. . . ." (IC p. 139, 148)

2.3 Endpoints and Measures

(a) What endpoints will be measured? Are they appropriate to the question(s) being asked?

"Biting pressure during the test day will be determined from the landing rate on the controls' arm during one minute periods for up to five minutes. . . . The landing rate verification will be conducted at, approximately, one-half hour intervals throughout each test day." (p. 31)

"A whole body count of mosquito landings on one of the control subjects will be taken at the initiation of the test and then hourly." (p. 31)

"Treated test subjects will expose their treated arms to mosquitoes at approximately 30 minute intervals. . . . The test subjects will expose treated arms until the FCB . . . or until 12 hours have elapsed, whichever occurs first." (p. 32) "We will promptly remove mosquitoes which do not have all six of their legs on your treated skin when

they attempt to bite, because we do not count the bites of mosquitoes which have one or more legs on the surrounding bandages when they bite your treated skin." (IC, p. 142, 151)

"ICR plans to evaluate repellency based on protection from bites rather than landings. Disease can only be transmitted by probes and bites, not by landings, so measuring repellency by bites is more realistic from a public health perspective than landings." (p. 14)

Landing pressure on untreated controls and FCB (First Confirmed Bite) on each treated arm are appropriate endpoints, but it isn't explained why landings are appropriate to verify "biting pressure" but bites are necessary to measure a failure of efficacy. Certainly a distinction between probes and bites is not justifiable on the basis of "realism from a public health perspective", since disease can be transmitted by either a probe or a bite. The practice of discounting bites from mosquitoes which do not have all six legs on the treated skin—described only in the IC, not in the protocol—is not explained or justified; again, from a public health perspective, the location of a biting mosquito's feet are of no consequence. No plan for utilizing the whole body count of mosquito landings is provided; it isn't clear how it could help answer the research question.

(b) What steps are proposed to ensure measurements are accurate and reliable?

- Two 'alternate' subjects will be enrolled to ensure adequate sample size
- All data recording will be done by investigators (p. 33)
- Subjects will work in pairs, checking each other as well as themselves for mosquito landings (p. 33)
- Bites will be verified by a research technician trained to recognize and discern between probes and bites (p. 33)

(c) What QA methods are proposed?

"Good Laboratory Practices will be followed throughout the study. The QAU representative will observe and write phase report(s) for this study. All data will be archived." (p. 34)

(d) How will uncertainty be addressed? Will point estimates be accompanied by measures of uncertainty?

"The time to first confirmed bite for all treated test subjects will be averaged and the standard deviation computed. A 95% confidence limit will be determined." (p. 34)

3. Subject Selection

3.1 Representativeness of Sample

(a) What is the population of concern? How was it identified?

The population of ultimate concern consists of people who would purchase and use insect repellents. Little information is available to characterize this population, but it is presumed that users of insect repellents are diverse in age, gender, physical size, general health, attractiveness to biting insects, and other characteristics.

(b) From what populations will subjects be recruited?

"ICR has been conducting repellent studies for over twenty years. During this time ICR has amassed a large list of potential study subjects. These subjects also refer friends and colleagues to us." (p. 27)

(c) Are expected participants representative of the population of concern? If not, why not?

"The database . . . that we select our subjects from, is as representative of potential repellent users as we are able to make it in terms of both practical and ethical considerations." (p. 20)

By excluding children, pregnant or nursing women, non-English speakers, and those in poor health, among others, the exclusion criteria will mean that participants will not be representative of at least some segments of the population of concern.

(d) Can the findings from the proposed study be generalized beyond the study sample? Yes.

3.2 Equitable Selection of Subjects

(a) What are the inclusion/exclusion criteria? Are they complete and appropriate?

Inclusion: "You must be between 18 and 65 years of age and consider yourself to be in good health." (p. 139)

"Test subjects must be able to read, speak, and understand English." (p. 26) "Test subjects must follow the requirements of the study as explained to them. . . . Test subjects must be attractive to mosquitoes, as evidenced by previous being bitten by mosquitoes. . . . Test subjects must wear proper protective clothing during the test, such as their own blue jeans, heavy socks, long sleeve shirts, and a headnet and gloves provided by ICR." (p. 27)

Note that vulnerability to West Nile Virus begins to increase at approximately age 50; an upper age bound of 65 is too high to be consistent with risk minimization for a field study of mosquito repellency. The criteria requiring following directions and

wearing appropriate protective clothing are misplaced in a discussion of eligibility; these are potential reasons why an eligible subject might be removed from the study.

Exclusion: pregnancy or breastfeeding; permanent full time employees of ICR, Inc.; sensitivity to mosquito bites, insect repellents, or skin care products; smoking or drinking alcohol within 12 h. before the test; use of perfumed cosmetics, skin creams, shaving lotion, etc. on the day of the test. (p. 27)

Eligibility criteria are listed in the protocol at two locations—first on p. 10 in a discussion of "Subjects", and then more formally on pp. 26-27. They are also listed in the IC documents (p. 139, 148). There are troubling inconsistencies between the multiple lists, which should be reconciled before the research goes forward.

The formal list of "ineligibility factors" on p. 27 excludes "permanent full time employee of ICR, Inc.". On p. 10 of the protocol the criterion is stated more inclusively: "full time employees of either ICR, Inc., or the sponsor." The possibility of coercion or undue influence is always a concern where employees are recruited as test subjects; that concern is not entirely laid to rest by a promise to exclude only "permanent full-time" employees. A more broadly worded exclusion of employees is appropriate, unqualified by whether they are temporary or permanent employees, or whether they are full-time or part-time employees, or whether they are employed by ICR, Inc. or by the sponsor. If all such employees are not excluded, their inclusion should be explicitly justified, and specific procedures should be described both to protect them from any element of coercion or undue influence and to protect the integrity of the research from any potential bias.

(b) What, if any, is the relationship between the investigator and the subjects?

Subjects are recruited from ICR's "large list of potential study subjects" and the "friends and colleagues" of those potential study subjects. (p. 27) At least "permanent full time employees" of ICR, Inc. are excluded; in alternate versions of the eligibility criteria the exclusion is stated to apply as well to all full-time employees of the sponsor as well as to employees of ICR.

(c) If any potential subjects are from a vulnerable population, what is the justification for including them?

The upper age bound for eligibility is 65. It is generally accepted that vulnerability to West Nile Virus is greater for those over about 50 or 55. Including subjects in the age range from 55-65 in a test of repellency of mosquitoes which could vector WNV is not consistent with risk minimization for those subjects. No justification is provided for setting the upper age range at 65.

(d) What process is proposed for recruiting and informing potential subjects?

The recruiting/informing process to be used is described in the protocol on pp. 21, 27-29 and in the IC documents (pp. 138-139; 147-148). See also discussion below in section 8(g).

(e) If any subjects are potentially subject to coercion or undue influence, what specific safeguards are proposed to protect their rights and welfare?

The inconsistencies among the statements of eligibility factors suggest that some employees of ICR (part-time or other than permanent full-time employees) might be recruited as subjects, as well as employees of the sponsor. These inconsistencies are not acknowledged, and neither justification for including employees nor specific safeguards to protect their rights and welfare are discussed.

3.3 Remuneration of Subjects

(a) What remuneration, if any, is proposed for the subjects?

"We will pay you $99/day ($11/hour) for every day you are away from home. In addition, we will pay you $16.50/hour on the study day for every hour beyond 9 hours that the study continues. The payment for a 12-hour test day will be $148.50 for 12 hours plus $16.50 for any additional hours beyond 12. . . . If we ask you to drop out of the test, and you have complied with all of our requests, we will still give you 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 stated hourly rate. We will attempt to transport you back to your home as soon as reasonably possible. If we cannot accomplish this, you will stay at our place of lodging until the end of the study. We will pay for your travel, lodging, and breakfast, lunch, and dinner costs." (p. 143, 151)

(b) Is proposed remuneration so high as to be an undue inducement?

"If you are chosen to participate in this study, you will be paid for a total of six days as discussed below." (p. 139, 148) The overall payment for six days, assuming 14 h. on the day of the test, would be $676.50. In addition, ICR promises to provide air travel to and from the test area, plus all expenses of lodging and meals. That may be high enough to serve as a considerable inducement to participate. Since, however, subjects are recruited from among previous subjects, it is unlikely that this remuneration would unduly influence someone to participate against his/her better judgment.

(c) Is proposed remuneration so low that it will only be attractive to economically disadvantaged subjects? No.

(d) How and when would subjects be paid?

"You will receive this payment by mail at the conclusion of the study." (p. 143, 152)

4. Risks to Subjects

4.1 Risk characterization

(a) Have all appropriate prerequisite studies been performed? What do they show about the hazards of the test materials?

"These proposed insect repellent formulations use the active ingredient, "Picaridin®, which was first registered by the US EPA under FIFRA on December 7, 2000. As required under FIFRA, registration of Picaridin® as an active ingredient is supported by an extensive data package that includes toxicity test data that demonstrate low acute and chronic toxicity." (p. 17)

"The inert ingredients in the test samples were selected because they are widely used in cosmetic and personal care formulations, are non-sensitizers, and experience has shown that their combination is both beneficial for skin care and safe for direct human exposure. To expedite product registration under FIFRA, the sponsor has confirmed that the inert ingredients have been previously reviewed and approved by EPA for use in FIFRA registered products." (p. 18)

It is true that EPA has registered other formulations of picaridin, but these two passages suggest erroneously that EPA registers ingredients—active and inert. EPA registers only products, and acute toxicity data on the two formulations proposed for testing in this research has not yet been submitted.

(b) What is the nature of the risks to subjects of the proposed research?

Risks are of three kinds: the risk of reaction to the repellents tested, the risk of reaction to arthropod bites, and the risk of contraction of an arthropod-borne disease.

"The active ingredient, Picaridin® demonstrates a low acute oral, dermal and inhalation toxicity. It is classed as Category IV for acute inhalation toxicity and primary dermal irritation. It is not a dermal sensitizer. . . . All of the inert ingredients used . . . have a long history of safe use in various personal care and cosmetics products. Moreover, the sponsor has confirmed that all of the inert ingredients used . . . have been previously reviewed and approved by EPA for use in FIFRA registered insect repellent products." (p. 23). "You may have a reaction to the test repellents. The Sponsor has minimized this possibility by choosing an active ingredient (picaridin) which has demonstrated low acute oral, skin, and inhalation toxicity. The Environmental Protection Agency (EPA) has classified it as Toxicity Category IV, low toxicity for acute inhalation toxicity and skin irritation. The Sponsor has selected the inert ingredients in the formulation because these inerts are widely used in cosmetic formulations, are not sensitizers, and experience has shown that their use is both beneficial for skin care and safe for direct human exposure." (IC, p. 143, 152)

The statements concerning EPA's assignment of Toxicity Category IV for two measures of acute toxicity may be true for other materials or products, but are misleading with respect to these test materials—especially in the Informed Consent document—and should be deleted. Based on EPA's knowledge of the acute toxicity profiles of similar picaridin formulations a more appropriate statement would mention that the formulations are eye irritants, assigned by EPA to Toxicity Category III.

"A bite occurs when a mosquito pierces your skin and takes blood. A probe is the same except it doesn't take blood. The irritation from a mosquito bite or probe may cause itching, redness or swelling that will usually disappear within a couple of days, or in severe cases may cause the development of large bumps on your skin, difficulty breathing, sweating and/or a rapid pulse." (IC p. 142, 151)

There is no discussion or characterization in the protocol of the risk of a reaction to mosquito bites—only assertions as to how the risk will be minimized.

"It is recognized that mosquitoes are vectors of many diseases. . . . Since the EPA requires demonstration of the repellency of mosquitoes known to carry specific diseases such as the WNV in order to substantiate related product claims, the sponsor is compelled to conduct field testing in areas in which test subjects will attract these potential vector species." (p. 24) "The disease risks you will be exposed to are primarily from the bites of mosquitoes. Fortunately, most of these diseases do not occur naturally in the United States, but diseases like malaria and dengue are occasionally introduced by travelers. Mosquitoes are also known to carry various types of encephalitis viruses such as West Nile Virus (WNV). The percentage of mosquitoes carrying WNV is small and most people who have developed serious symptoms have been the elderly or those with compromised immune systems. The most common symptoms of WNV are mild illness with fever, headache, and body aches. The principal carriers of the WNV are not common at the test site. You may also be exposed to deer ticks which can carry Lyme's Disease." (IC p. 142, 151)

(c) What is the probability of each risk associated with the research? How was this probability estimated?

No numerical probability is estimated. "The CDC estimates that only about 1 in 5 people who contract WNV will be affected. About on in 150 people infected with WNV will develop severe illness and about 4 of 5 will show no symptoms. . . . The principal carriers of the WNV belong to the *Culex* genus. . . . This particular genus of mosquitoes is not common in areas where we will be conducting the study. While the risk of contracting WNV is considered to be low, no guarantees can be offered." (p. 24)

Potential subjects are told with respect to the risks of contracting an arthropod-borne disease at the Georgia test site "Georgia reported 8 cases of WNV, one case of Eastern Equine Encephalitis, and one case of La Crosse Encephalitis in 2006. . . . Of

the 8 cases of WNV in Georgia, one . . . was reported for Chatham County, the Georgia site of the study." (IC p. 142). In a parallel passage for the Florida test site subjects are told "Florida reported 3 cases of WNV, one case of Eastern Equine Encephalitis, and no other arbovirus type cases in 2006. None of these cases occurred in Lee County, the proposed study site." (IC p. 151)

4.2 Risk minimization

(a) What specific steps are proposed to minimize risks to subjects?

- Candidates with known allergic reactions to insect repellents or skin care products are excluded. (p. 23)
- Subjects "will be monitored throughout the study and prompt medical attention will be obtained if any adverse reaction is observed." (p. 23)
- Candidates "known to have severe reactions to mosquito bites" are excluded. (p. 23)
- Subjects will be instructed to cover exposed skin "immediately upon receiving a FCB on that area." (p. 23)
- Subjects will expose "only a small area (250 cm^2) of skin on each arm" for five minutes of every thirty during the test. Other parts of the body will be protected with provided gloves and headnets (p. 23) and two layers of their own clothing (IC p. 142, 151; not mentioned in protocol).
- Subjects will be teamed with a partner for joint observation; experienced technical personnel will be present at all times to assist.
- At the end of each 5-minute exposure period staff will lead subjects "out of the study site to an area where mosquitoes are not prevalent, possibly a screened enclosure." (IC p. 141, 150)
- Field tests are conducted in areas where West Nile virus has not been detected by the local Mosquito Abatement District for at least a week. (p. 24)
- Minimum controls: two untreated controls per site to confirm biting pressure; no positive controls.
- Exposure of untreated controls for no more than 5 min/half hour; exposed skin may be covered immediately following the fifth landing. (p. 31)
- First Aid materials and First-Aid qualified staff will be available on-site.
- Subject and staff shoes will be treated with permethrin to repel ticks; subjects will be examined for ticks at end of study day. (p. 33)
- Study staff will brush away mosquitoes with fewer than all six of their legs on treated skin. (IC p. 141, 150)
- A local hospital will receive prior notification of the study. (p. 25)
- Cell phones available to make emergency calls.

(b) How do proposed dose/exposure levels compare to established NOELs/NOAELs for the test materials?

At the proposed dose rate each treated subject will receive some 833 mg repellent applied to 500 cm^2 skin. The concentration of picaridin in the test materials is not

greater than the 20% previously registered by EPA in other products; assuming 20% picaridin as the worst case, 833 mg product would be equivalent to 167 mg picaridin. Because of the ethanol in the formulations this figure is adjusted by an "ethanol enhancement" factor of 2.26, yielding an adjusted dose of 377 mg, or 5.4 mg/kg for a 70 kg adult. The NOAEL for acute dermal toxicity in the rat for picaridin is 5000 mg/kg bodyweight, picaridin is less readily absorbed by human skin than by rat skin, and we do not expect the inert ingredients other than ethanol to affect the systemic dermal toxicity. Thus the estimated margin of exposure for picaridin acute dermal toxicity is not less than—and may be substantially greater than—5000/5.4 or 926.

(c) What stopping rules are proposed in the protocol?

"The test will be terminated on a treated arm when a bite is followed by one additional bite . . . within one 5 minute exposure period or . . . in each of two consecutive exposure periods. . . .

"The study could be cancelled for several reasons; the first would be inclement weather. If weather conditions on site present unsafe circumstances for test personnel the study will be cancelled. These conditions included severe storm threats, high wind, or threat of lightning.

"Additional reasons for test cancellation would be insufficient target insect activity. Any health concerns, the presence of WNV, or test material related reactions could also be reason for cancellation." (p. 32)

(d) How does the protocol provide for medical management of potential illness or injury to subjects?

"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 by either ICR staff or professional ambulance." (p. 25)

(e) How does the protocol provide for safety monitoring?

"Further, the subjects will be closely monitored during the study for signs of significant skin reactions and prompt medical attention will be obtained should an adverse reaction be experienced." (p. 14)

(f) How does the protocol provide for post-exposure monitoring or follow-up? Is it of long enough duration to discover adverse events which might occur?

The protocol does not discuss post-exposure monitoring or follow-up.

(g) How and by whom will medical care for research-related injuries to subjects be paid for?

"If any test subjects need medical attention, their medical care will be paid by ICR." (p. 25)

"We will pay all of your medical bills for study-related illnesses and injuries." (IC p. 143, 152)

5. Benefits

(a) What benefits of the proposed research, if any, would accrue to individual subjects?

"You will probably get no personal benefit from this study." the results of the study may help bring a new repellent to the market and thus provide consumers with a greater choice of repellents." (IC p. 143, 152)

(b) What benefits to society are anticipated from the information likely to be gained through the research?

"While there is obviously an economic incentive to the sponsor of the study to offer a new insect repellent alternative to consumers, such products must offer a recognized benefit to consumers or they will simply not be purchased or used. It is important to bring new insect repellent products to market so that consumers have alternatives that they find personally acceptable and convenient to use to protect themselves and family members from irritating and potential disease-carrying insect bites. New products, such as the proposed test samples, have been formulated to provide protection from insect bites in combination with other benefits that promote consumer acceptance and use of the product (i.e., convenience of product form or method of application, fragrance preferences, preference for, or avoidance of, a specific active ingredient, etc.)." (p. 14)

"While you will probably get no personal benefit from this study, the results of the study may help bring a new repellent to the market and thus provide consumers with a greater choice of repellents." (IC p. 143, 152)

(c) How would societal benefits be distributed? Who would benefit from the proposed research?

The direct beneficiary of the research is likely to be the sponsor. Assuming eventual regulatory approval, indirect beneficiaries would include those repellent users who prefer the new formulations to previously available repellents.

(d) What is the likelihood that each identified societal benefits would be realized?

The testing is likely to demonstrate that the new formulations are effective, and thus the sponsor is likely to realize a direct benefit from the research. Realization of other societal benefits will depend on consumer acceptance of the new formulations.

6. Risk/Benefit Balance

(a) How do the risks to subjects weigh against the anticipated benefits of the research, to subjects or to society?

The protocol reduces but does not minimize the risks to subjects. In particular, risks of both irritation and disease from mosquito bites could be further reduced by treating landings as evidence of a failure of efficacy, rather than only bites. The exclusion as evidences of efficacy failure of landings, probes, and bites with fewer than all six legs of a biting mosquito on the treated skin serves not to make the study more "realistic from a public health perspective" (as is asserted in the protocol) but to make it both riskier for the subjects and a less demanding test of product performance. Additional opportunities to further reduce risks to subjects include an improved medical management plan, more thoughtful attention to stopping rules, and provision for post-exposure follow-up.

There are no direct benefits of this research to the subjects, so justification depends on the anticipated benefits to society from the information likely to be gained. The protocol discussion of benefit does not address the benefits of the knowledge likely to be gained from the research, but instead asserts the benefit of bringing alternative repellents to market. Since these test materials fall within the ranges of picaridin concentration and product forms EPA has previously accepted for registration, they are likely to differ only slightly from others already in the market.

Notwithstanding the weaknesses of the arguments concerning the expected benefit of this research, there is potential societal benefit in a wide range of differing effective repellent products, both from a public health perspective and from a nuisance-reduction perspective. If the risks to subjects are further reduced as suggested above, the residual risks are likely to be reasonable in light of the potential benefit to consumers of a wider range of choice in effective mosquito repellents.

7. Independent Ethics Review

(a) What IRB reviewed the proposed research?

Essex Institutional Review Board, Inc., Lebanon NJ

(b) Is this IRB independent of the investigators and sponsors of the research? Yes

(c) Is this IRB registered with OHRP? Yes

(d) Is this IRB accredited? If so, by whom?

"This IRB is accredited by PHRP, and is in the process of obtaining accreditation from AAHRPP." (p. 20)

EIRB does not appear in the list of accredited organizations on the PHRP website (www.phrp.org). EIRB does not appear on the list of accredited organizations on the AAHRBB website (www.aahrpp.org).

(e) Does this IRB hold a Federal-Wide Assurance from OHRP?

Not reported. EIRB is not listed as holding an FWA on the OHRP website.

(d) Are complete records of the IRB review as required by 40 CFR 26.1125 provided?

The transmittal of the protocol and related materials to the IIRB, the IIRB's approval letter, and minutes of the IIRB discussion are provided.

Documentation of IRB procedures was not provided, and a statement is included from the investigators that procedures are available for inspection only at the EIRB site.

(e) What standard(s) of ethical conduct would govern the work?

"ICR, Inc., (ICR) policy complies with the Department of Health and Human Services Policy at 45 C.F.R. pt. 46 and 45 C.F.R. §§ 46.109, 46.116, and the EPA Part 26 model rule at 40 C.F.R. pt 26 subparts K and L, when human volunteers are used. Thus ICR submits a protocol, informed consent document, and standard indemnification forms to an independent institutional review board (IRB) set up to ensure that the rights and welfare of the participants are protected and that the study is carried out in an ethical manner." (pp. 19-20)

8. Informed Consent

(a) Will informed consent be obtained from each prospective subject? Yes.

(b) Will informed consent be appropriately documented, consistent with the requirements of 40 CFR 26.1117? Yes.

(c) Do the informed consent materials meet the requirements of 40 CFR 26.1116, including adequate characterization of the risks and discomforts to subjects from participation in the research, the potential benefits to the subject or others, and the right to withdraw from the research? Yes.

(d) What is the literacy rate in English or other languages among the intended research subjects?

100%. English literacy is a requirement for participation.

(e) What measures are proposed to overcome language differences, if any, between investigators and subjects? n/a

(f) What measures are proposed to ensure subject comprehension of risks and discomforts?

Opportunities to ask questions.

(g) What specific procedure will be followed to inform prospective subjects and to seek and obtain their consent?

"The Informed Consent Document will be formally explained to all the test subjects before the study is scheduled to begin. If any test subject refuses to sign after learning the details of the document, they will not be allowed to participate in the study. To try to avoid this inconvenience, the informed consent will be explained to each test subject, either in person, on the telephone, and by mailing ICDs prior to the study, to try to eliminate any potential test subject not interested in the project." (p. 21)

"During the recruitment process, interested potential subjects will have an Informed Consent Document (ICD) mailed to them if required. ICR will call to confirm receipt of ICD. They will be instructed to contact the Principle Investigator (P.I.) to verify receipt of the ICD and to ask any ICD or study related questions.

"All interested people will be offered the opportunity to come to ICR to go through the consent process in person.

"The P.I. will contact all interested subjects by phone several days after receipt of the ICD to fully explain the ICD by reading it to them. Sufficient time will be spent with each interested subject to answer any questions they may have. They will then be invited to sign the ICD. Each consenting subject will be asked to sign and date the ICD in the presence of a witness. The witness will then sign and date the ICD> Each consenting test subject will be asked to mail the signed ICD back to ICR." (p. 15)

"When a repellent study date has been established, ICR will contact potential study subjects by telephone and briefly discuss the study, the date of the study, and location. . . . ICR uses the following initial telephone script to recruit test subjects:

> 'ICR will be conducting a repellent project on these dates, (month, Day(s), Year), at (exact study site) would you be available to participate in this study?'

"If the potential test subject is available, the inclusion/exclusion criteria will be discussed in detail and verified whether the subject qualifies to participate. The ICD will also be

discussed with the test subject at this time. In addition, ICR will mail a copy of the ICD to each interested test subject for their review. They will be instructed to contact the P.I. to verify receipt of the ICD and to ask any ICD or study related questions they may have.

The P.I. will contact all interested subjects by phone several days after receipt of the ICD to full explain the ICD with them. All contacted people that show interest will be offered the opportunity to come to ICR to go through the consent process in person. If interested subjects are unable to travel to ICR, the consent process will be conducted on the phone. Sufficient time will be spent with each interested subject to answer any questions they may have. When both the P.I. and the interested subject are satisfied that they have meet the study qualifications for inclusion into the study, understand and are comfortable with the ICD, they will then be invited to sign the ICD. Each subject will be asked to sign and date the ICD in the presence of a witness. Their signature will acknowledge that they have been informed and freely give their consent to participate in the study. The witness will then sign and date the ICD. Each test subject giving their consent by phone will be asked to mail the signed ICD back to ICR." (pp. 27-28)

See also Informed Consent Form, pp. 138-154

(h) What measures are proposed to ensure fully voluntary participation and to avoid coercion or undue influence?

Candidates are offered opportunities to decide not to participate; participants are offered opportunities to withdraw. Exclusion factors rule out participation by permanent full-time employees of ICR. Recruitment of alternate subjects ensures that subjects will not be reluctant to withdraw lest the validity of the investigation be compromised.

9. Respect for Subjects

(a) How will information about prospective and enrolled subjects be managed to ensure their privacy?

All data collection forms include spaces for both subject name and subject signature. It would provide greater assurance of privacy to identify subjects by code on all but one master directory that links names to codes. Subjects are told they will be identified by first name and the first initial of their last name in reports of the study. (IC p. 144, 153). Recruitment of alternate subjects provides an opportunity for discrete withdrawal without explanation.

"Females will be required to perform an over the counter pregnancy test . . . . on the morning of the test. The results will be verified by a qualified female ICR staff member. . . . The results of this pregnancy test will be kept confidential and will not be disclosed to anyone other than the test subject and the P.I.." (p. 30)

(b) How will subjects be informed of their freedom to withdraw from the research at any time without penalty?

Subjects are so informed in the recruitment process and in the Informed Consent Form.

(c) How will subjects who decline to participate or who withdraw from the research be dealt with?

Subjects who decide not to participate will simply go their way. Subjects who withdraw from the research will be paid for their time (IC p. 143, 152). "If you are already at the test site when you decide to drop out of the study, we will attempt to transport you back to your home. If we cannot accomplish this, you will stay at our place of lodging until the end of the study." (IC p. 144, 153)

§ 26.1111 Criteria for IRB approval of research
ICR Protocol No: G0590307001A044 (Version of 4/11/2007)

Criterion	Y/N	Comment/Page Reference
(a)(1)(i) Risks to subjects are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk.	Y	
(a)(1)(ii) Risks to subjects are minimized, whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.	N/A	
(a)(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.	Y	
(a)(3) Selection of subjects is equitable, taking into account the purposes of the research and the setting in which it will be conducted, and being particularly cognizant of the special problems of research involving vulnerable populations, such as prisoners, mentally disabled persons, or economically or educationally disadvantaged persons.	Y	
(a)(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by §26.1116.	Y	
(a)(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by §26.1117.	Y	
(a)(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.	Y	
(a)(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.	Y	
(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, additional safeguards have been included in the study to protect the rights and welfare of these subjects.	N/A	

§26.1116 General requirements for informed consent
ICR Protocol No: G0590307001A044 (Version of 4/11/2007)

Criterion		Y/N	Comment/Page Reference
No investigator may involve a human being as a subject in research covered by this subpart unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative		OK	All subjects will provide legally effective informed consent.
An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence		OK	The procedure described in protocol pp. 27-29 provides sufficient opportunity to consider. . . and minimizes the possibility of coercion or undue influence.
The information that is given to the subject or the representative shall be in language understandable to the subject or the representative		OK	Information is presented in English
No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence		OK	The IC contains no exculpatory language
(a) In seeking informed consent the following information shall be provided to each subject	(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental	OK	p. 138; 147
	(2) A description of any reasonably foreseeable risks or discomforts to the subject	OK	pp. 142-143; 151-152
	(3) A description of any benefits to the subject or to others which may reasonably be expected from the research	OK	p. 143; 152
	(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject	OK	p. 144; 153
	(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained	OK	p. 144; 153
	(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained	OK	Compensation p. 143; 152 Treatment p. 143;152
	(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject	OK	p. 144; 153
	(8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled	OK	p. 144; 153
(b) When appropriate, one or more of the following elements of information shall also be provided to each subject	(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject may become pregnant) which are currently unforeseeable	N/A	
	(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent	OK	p. 143; 152
	(3) Any additional costs to the subject that may result from participation in the research	N/A	
	(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject	N/A	
	(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject	N/A	
	(6) The approximate number of subjects involved in the study	OK	p. 139; 148
(e) If the research involves intentional exposure of subjects to a pesticide, the subjects of the research must be informed of the identity of the pesticide and the nature of its pesticidal function.		OK	p. 143; 152

§26.1117 Documentation of informed consent
ICR Protocol No: G0590307001A044 (Version of 4/11/2007)

Criterion	Y/N	Comment/Page Reference
(a) Informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form.	OK	Form pp. 138-154 Procedures pp. 27-29
(b)(1) The consent form may be a written consent document that embodies the elements of informed consent required by §26.1116. This form may be read to the subject or the subject's legally authorized representative, but in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed; or	OK	Proposed IC form meets requirements of §26.1116; procedure described in protocol pp. 27-29 provides adequate opportunity to read it before it is signed.
(b)(2) The consent form may be a short form written consent document stating that the elements of informed consent required by §26.1116 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative, in addition to a copy of the short form.	N/A	

40 CFR 26.1125 Submission of proposed human research for EPA review
ICR Protocol No: G0590307001A044 (Version of 4/11/2007)

Any person or institution who intends to conduct or sponsor human research covered by §26.1101(a) shall, after receiving approval from all appropriate IRBs, submit to EPA prior to initiating such research all information relevant to the proposed research specified by §26.1115(a), and the following additional information, to the extent not already included:

	Requirement		Y/N	Comments/Page Refs
The following Information, to the Extent not already included:	§1125(a) a discussion of:	(1) The potential risks to human subjects	Y	pp. 13-14, 23-26 and IC
		(2) The measures proposed to minimize risks to the human subjects;	Y	pp. 23-26 and IC
		(3) The nature and magnitude of all expected benefits of such research, and to whom they would accrue	Y	pp. 14, 26
		(4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and	Y	p. 19
		(5) The balance of risks and benefits of the proposed research.	N	No discussion weighing risks and benefits provided
	§1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB.		Y	Approved versions pp. 138-154. Prior versions also provided
	§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.		Y	pp. 27-29. No advertisements used
	§1125(d): A description of the circumstances and methods proposed for presenting information to potential human subjects for the purpose of obtaining their informed consent.		Y	pp. 27-29 and IC
	§1125(e): All correspondence between the IRB and the investigators or sponsors.		Y	pp. 9, 67-111, 128-137
	§1125(f): Official notification to the sponsor or investigator. . . that research involving human subjects has been reviewed and approved by an IRB.		Y	pp. 136-137
all information relevant to the proposed research specified by § 26.1115(a)	(1) Copies of • all research proposals reviewed by the IRB, • scientific evaluations, if any, that accompanied the proposals reviewed by the IRB, • approved sample consent documents, • progress reports submitted by investigators, and reports of injuries to subjects.		Y n/a Y n/a	pp. 11-66 None accompanied the proposal pp. 138-154 Initial review of new proposal
	(2) Minutes of IRB meetings . . . in sufficient detail to show • attendance at the meetings; • actions taken by the IRB; • the vote on these actions including the number of members voting for, against, and abstaining; • the basis for requiring changes in or disapproving research; • a written summary of the discussion of controverted issues and their resolution.		Y Y Y N n/a	IRB minutes pp. 104-107 Basis for required changes not reported No controverted issues
	(3) Records of continuing review activities.		n/a	n/a for protocols
	(4) Copies of all correspondence between the IRB and the investigators.		Y	Provided by investigator; pp. 9, 67-111, 128-137
	(5) • A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; • any employment or other relationship between each member and the institution, for example, full-time employee, a member of governing panel or board, stockholder, paid or unpaid consultant.		Y Y	pp. 156-157
	(6) Written procedures for the IRB in the same detail as described in §26.1108(a) and §26.1108(b).		N	Asserted to exist (p. 159) and to be available for inspection on site (p. 7B). Previously submitted to EPA.
	(7) Statements of significant new findings provided to subjects, as required by §26.1116(b)(5).		n/a	n/a for protocols