UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

MEMORANDUM:

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

September 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.; Gaynor, W. (2007) Protocol for Evaluating the Efficacy of Personal Repellents Against Mosquitoes in the Laboratory Including Supporting Materials Satisfying 40 CFR §26.1125 for Avon Skin-So-Soft SSS Bug Guard Plus Picaridin Insect Repellent (EPA Reg. No. 806-29) and Avon Skin-So-Soft SSS Bug Guard Plus Picaridin Insect Repellent Spray (EPA Reg. No. 806-31). Unpublished document dated August 8, 2007, prepared by Insect Control & Research, Inc., under Protocol ID G0590607001A117. 95 p.

We have reviewed the referenced protocol for a laboratory test of mosquito repellency from both scientific and ethics perspectives. Scientific aspects of the proposed research are assessed in terms of the recommendations of the draft EPA Guidelines §810.3700 and of the EPA Human Studies Review Board. Ethical aspects of the proposed research are assessed 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 nature and magnitude of all expected benefits of such research, and to whom they would accrue, as required by 40 CFR §26.1125(a)(3). The discussion of benefits on p. 23 is irrelevant to this protocol, addressing only the benefits of new repellent products; the test materials in this case are already registered.

- A discussion of the balance of risks and benefits of the proposed research, as required by 40 CFR §26.1125(a)(5).

- A description of the circumstances and methods proposed for presenting information to potential human subjects for the purpose of obtaining their informed consent, as required by 40 CFR §1125(d).

- Written procedures for the IRB in the same detail as described in §26.1108(a) and §26.1108(b). Although the rule requires that the IRB procedures be submitted, and although the investigators (p. 6)[1] report 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. 10-34) the submitted package included the following supporting documents—all considered in this review:

- Statement of No Confidentiality Claims (p. 2)
- Promise of GLP Compliance (p. 3)
- 40 CFR §26.1125 checklist and related comments (pp. 4-6)
- Chronology of ICR:EIRB Correspondence (p. 7)
- Initial transmittal of protocol to EIRB (p. 9)
- Informed Consent Documents (CDs)
    - As initially submitted to the EIRB (pp. 36-41)
    - As revised 8/2/07 and resubmitted to the EIRB (pp. 75-80)
    - As approved by EIRB 8/7/07 (pp. 85-90)
- Site Application Letter as initially submitted to the EIRB (pp. 43-48)
- Curriculae vitae of Principal and other Investigators (pp. 49-56)
- MSDSs for test materials (pp. 57-62)
- Indemnification Agreements Avon/ICR (p. 63) and Avon/EIRB (p. 64)
- "Investigator Attestation of Qualifications" (p. 65)
- "Investigator Conflict of Interest Declaration" (p. 66)
- Proposed amendments 1-8 8/2/07 responsive to EIRB comments (pp. 73-74)
- EIRB approval letter of 8/7/07 (p. 82)
- Amendments 1-8 with EIRB approval stamp 8/6/07 (pp. 83-84)

[1] Many sections of the submission are paginated more than once; all page references in this review are to the "*N* of 95" page number.

- EIRB Membership Lists (pp. 92-94
- EIRB "Statement of Compliance" (p. 95)

ICR's assessment of the responsiveness of this submission to the requirements of 40 CFR §26.1125 (pp. 4-6) differs markedly from EPA's. Among the more significant differences are that ICR defined everything sent to the IRB as "correspondence"—including the protocol, consent documents, application forms, MSDSs, etc., and that ICR cites all three versions of the consent documents as responsive to the requirements of §26.1125(a)(1) – (5) for discussions of risk, risk minimization, benefits and their distribution, alternative means of getting comparable information, and risk/benefit balance. EPA has applied a much narrower definition of correspondence, and does not consider the content of consent documents required by 40 CFR §1116 to meet the requirements of §26.1125(a).

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 registered topical picaridin-based repellents against *Culex quinquefasciatus* mosquitoes in the laboratory for up to 8 hours. EPA requires product-specific laboratory efficacy data with *Culex* sp. to support label claims of repellent efficacy for more than 4 hours against "mosquitoes which can vector West Nile virus." Although these materials have previously been tested in the field for efficacy against other genera of mosquitoes, they have not previously been tested against *Culex*.

   The protocol discussion of societal benefit of the proposed research addresses only the value of bringing new repellents to market; this is irrelevant to this case, in which the repellents to be tested are already in the market. Notwithstanding the inadequate discussion of benefits, there are potential societal benefits from testing to identify registered repellents which are effective against potential vectors of WNV.

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." Children, adults over 55, pregnant or nursing women, non-English speakers and those in poor health are excluded as subjects. The sample will thus not be fully representative of the population of potential repellent users. One subject selected by lot will serve as an untreated control to verify aggressiveness of the caged mosquitoes.

   There is no indication that any subjects will be from populations potentially vulnerable to coercion or undue influence. All employees and relatives of employees of ICR, of the sponsor, or of any other interested party are excluded as subjects.

Subjects who complete the one-day test would be paid $99. Subjects would be responsible for their own transportation to the ICR laboratory.

3. **Risks to Subjects:** Risks of three kinds are discussed: the risk of reaction to the repellents tested, the risk of reaction to mosquito bites, and the risk of contracting a mosquito-borne disease.

    - 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 835 mg repellent applied to 500 cm^2 skin[2]. The concentration of picaridin in the test materials is 10%; thus 835 mg product is equivalent to 83.5 mg picaridin. Because the ethanol in the formulations increases percutaneous absorption, this figure is adjusted by an "ethanol enhancement" factor of 2.26, yielding an adjusted dose of 189 mg, equivalent to 2.7 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—5000/2.7, or 1,852.

    - Risks of mosquito 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 minimizing the number of untreated control subjects, and by exposing the untreated control subject only long enough to confirm continued mosquito landing pressure and encouraging the control subject to shake off landing mosquitoes before they can bite. Further reduction in risks of mosquito bites would be possible by treating landings as evidence not only of biting pressure but of efficacy failure as well.

    - The risk of contracting a mosquito-borne disease is characterized in the protocol as zero, because the mosquitoes are laboratory-reared and disease-free, and will not have had a blood meal. This class of risk is not mentioned to subjects in the consent document.

    - Additional risk-reduction measures proposed include providing for 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 consent document states that participating in the research will be of no benefit to subjects, but identifies no other beneficiaries or benefits. The protocol

[2] The standard dose rate is 1.67 mg/cm^2. Treated area is 250 cm^2 on each forearm, or 500 cm^2. Total dose of product for each subject is thus 1.67 x 500 = 835 mg.

acknowledges that the research will benefit the sponsor, but irrelevantly discusses the societal benefit of new products.

Assuming the testing shows good efficacy and supports regulatory approval of additional label claims, the direct beneficiary of the research is likely to be the sponsor, who is likely to realize increased sales. Indirect beneficiaries would include repellent users who prefer a repellent which has been shown to be effective against the kind of mosquitoes which vector WNV.

5. **Risk/Benefit Balance:** The protocol reduces but does not minimize the risks to subjects. In particular, the risk of a reaction to mosquito bites could be further reduced by interpreting landings as evidence of failure of efficacy, rather than only bites. Excluding landings and probes as evidences of efficacy failure makes the study both riskier for the subjects and a less demanding test of product performance.

   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 are already registered and in the market, such benefits cannot result from this research.

   Notwithstanding the weaknesses of the arguments concerning the expected benefit of this research, there is potential societal benefit in identifying registered repellents which are effective against *Culex* mosquitoes. 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.

6. **Independent Ethics Review:** The protocol has been reviewed and approved by Essex Institutional Review Board (EIRB) of Lebanon, NJ. EIRB is registered with the federal Office of Human Research Protections (OHRP), but does not hold a Federal-Wide Assurance. Although the protocol asserts that EIRB is accredited by PHRP, EIRB does not appear among the accredited organizations listed 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 this writing EIRB is not on the list of accredited organizations on the AAHRPP website (www.aahrpp.org). AAHRPP does not identify entities for which accreditation is pending.

   Minutes are provided of the EIRB meeting on July 30, 2007, at which this protocol was discussed. They do not explain the basis for requiring changes in the protocol and informed consent document, but since EIRB requested only minor editorial changes this is not a serious deficiency. Amendments 1-8 as reviewed and approved by EIRB address some but not all of the comments and requests made by EIRB in their meeting report. An integrated revision to the protocol incorporating amendments 1-8 has not been submitted.

   The discussion of ICR policies and their compliance with EPA's regulations, in suggesting that compliance only requires ICR to submit "all necessary documentation to

an independent institutional review board," suggests some confusion about what those rules require. In this same passage the criteria for IRB approval of proposed research, defined at 40 CFR §26.1111, are mischaracterized.

7. **Informed Consent:** The protocol as submitted includes two preliminary versions of the informed consent document as well as the final version approved by the EIRB. The final approved consent form satisfies the applicable requirements of 40 CFR §26.1116 and §26.1117, with the exception of the requirement of §26.1116(d) for a "description of any benefits to the subject or to others which may reasonably be expected from the research." As noted above, the consent document identifies no expected benefits or beneficiaries of the proposed research.

   Potential subjects are initially contacted by telephone from a database of former subjects of repellency tests. Those who are available to come to the ICR laboratory at the time the research is planned, who are "interested" in participating, and who meet the eligibility criteria are provided a copy of the consent document, either in person (if the candidate lives in the Baltimore area and is willing to travel to the ICR laboratory) or by mail. After confirming receipt of the consent document the P.I. discusses it with the candidate—in the ICR lab or by telephone—and answers any questions. The candidate then may choose to sign the IC document, but must sign it in the presence of the P.I. or another ICR researcher. After the P.I. signs it as well, a copy is provided to the subject.

   The process of informing candidates and seeking their consent is described only sketchily in the protocol. Clarification of the timing of the consent discussion and greater care in distinguishing between candidates and enrolled subjects is needed before the research goes forward.

8. **Respect for Subjects:** Methods proposed for managing information about prospective and enrolled subjects will generally protect their privacy from compromise. Notwithstanding the assurance that subjects will be identified only by their initials and a unique coded identifier, the control data collection form includes a space for subject signature. This is unnecessary, and it should be deleted.

   "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.." Planned recruitment of extra alternate subjects provides an opportunity for discrete withdrawal without explanation.

   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. A point-by-point evaluation of how the requirements of 40 CFR 26 Subparts K and L and the additional criteria recommended by the HSRB are addressed is appended as Attachment 1.

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

- The largely irrelevant protocol discussion of benefits of the research and to whom they would accrue should be replaced by a discussion of expected benefits acknowledging that the test repellents are already registered. The expected benefits and beneficiaries of the research should also be identified in the consent document.

- A discussion of the relation of risks and benefits should be added to the protocol

- Risks of reaction to mosquito bites could be further reduced by treating landings and probes as evidence not only of biting pressure but of efficacy failure as well. The end-point should either be changed to landings, or the requirement for bites must be justified by more than ICR's stated preference.

- The process of informing candidates and seeking their consent is described sketchily, and needs to be expanded, especially to clarify the sequence of steps and when they will occur. Until a subject signs the consent form and is enrolled, he or she remains simply a candidate. There is no intermediate status of "interested" candidate, or "committed" candidate.

- The control data collection form should identify the subject only by code or initials; the blank for subject signature must be deleted.

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 efficacy in the laboratory against *Culex quinquefasciatus* mosquitoes of two registered repellent products containing 10% picaridin as the sole active ingredient. The purpose of the study is to establish the mean time to first confirmed bite for each formulation under laboratory conditions, to support proposed label amendments to add claims of efficacy against mosquitoes which can carry or transmit West Nile virus (WNV).

1. **Study design:** The objective of the study is to determine efficacy of two registered mosquito repellent formulations containing picaridin against *Culex quinquefasciatus* under laboratory conditions. The objectives of the study can be met as proposed and will support calculations of (Complete) Protection Time for each formulation based on the mean time to First Confirmed Bite. Testing will be conducted in cages measuring 2 x 2 x 2 feet. Before the onset of testing, 100 3- to 8-day-old female mosquitoes which have not had a blood meal will be released into each cage. (EPA Guidelines recommend 200 mosquitoes per cage; the proposal to use only 100 per cage is not explained or justified.) One untreated control subject, selected by lot, will place an untreated forearm into each cage every 30 minutes during the test to confirm continued aggression of the test mosquitoes. Acceptable aggression is defined as 5 landings in 60 seconds on the exposed 250 cm^2 of skin of the untreated subject; if this rate of landings is not achieved, 100 more fresh mosquitoes will be released into each cage. The untreated control subject will shake off landing mosquitoes to minimize biting. Mosquitoes landing on the control subject are not aspirated in order not to reduce the number of host-seeking mosquitoes in each cage. No positive control treatment is proposed. The test is subject-blinded; the two 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. Ten to twelve subjects, each treated with both test products, will expose their forearms for 5 minutes at 30 minute intervals until they experience a confirming bite or until the end of the 8-hour test period—whichever comes first. Upon experiencing a confirming bite on one arm, that arm will not be tested further; the subject's other arm will continue to be tested until efficacy breakdown or 8 hours.

2. **Statistical Design:** The proposed sample size is ten for each test product—greater than the minimum of six recommended by EPA Guidelines, large enough to ensure robust averages across subjects, but small enough to be economical. Although the experimental design calls for ten treated subjects, twelve subjects will be treated with both test formulations—one on each forearm. Use of two more treated test subjects than are required will help to ensure a minimum "*N*" of ten, even if some subjects withdraw.

   No statistical comparisons of treated subjects to the untreated control are proposed. Repellency will be reported as "Protection Time" (PT), defined to be equivalent to "Complete Protection Time" (CPT) as defined in EPA Guidelines. CPT 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. If the distribution is non-normal, the protocol describes data transformations that will be considered in order to analyze the above data. For

"significantly skewed" data, central tendency will be described by the median and confidence intervals will be calculated using percentile ranks. It is unclear how these statistical evaluations will be applied to repellent success or failure, because the protocol also includes a discussion of nonparametric testing in which Cochran's Q Test will be applied to the collected data. This test focuses on changes in the proportions at each test interval over time. A degradation curve will also be plotted from the raw data.

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. No dosimetry study to establish typical consumer doses for each tested repellent is proposed. The standard dose of 418 mg of repellent will be applied by an ICR technician to a masked-off 250 cm2 area on each forearm of each treated subject. Treatments will remain in place for up to 8 hours.

4. **Endpoints and Measures:** The endpoint is Protection Time (PT). PT will be calculated as the mean time from initial application of the test formulation to the First Confirmed Bite (FCB). A FCB is defined as the "a bite which is followed by another bite in either the same 5 minute exposure period or the next consecutive 5 minute exposure period". For consistency with other repellent study data, EPA recommends that the endpoint be called "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 objective and explicit hypothesis
- 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 sample size
- Rationale for use of one untreated subject to monitor aggressiveness of test mosquitoes.

The following elements in the protocol require revision before the research goes forward:

- Information on diagnostic testing for normality and information on how to analyze non-normally distributed data is incomplete. Revise the explanation of how the results of the statistical analyses will be applied to determine repellent .protection time.

- Justification for using a mosquito population cage density that is less than the EPA Guideline Recommendations is required.

- EPA-registered product labels should be appended to the protocol.

Attachments:

1. Summary Review of ICR Protocol ICR G0590607001A117 dated 8/8/07
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 G0590607001A117

Title: Protocol for Evaluating the Efficacy of Personal Repellents Against Mosquitoes in the Laboratory Including Supporting Materials Satisfying 40 CFR §26.1125 for Avon Skin-So-Soft SSS Bug Guard Plus Picaridin Insect Repellent (EPA Reg. No. 806-29) and Avon Skin-So-Soft SSS Bug Guard Plus Picaridin Insect Repellent Spray (EPA Reg. No. 806-31).

Date: 8 August 2007

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1. Societal Value of Proposed Research

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

"Hypothesis: The repellent samples are expected to provide 8 hours of personal protection from *Culex quinquefasciatus* mosquitoes, a West Nile virus vectors, in the laboratory." (p. 12)

"The objective of the study is to determine the mean protection time from bites provided by the test articles under laboratory conditions to confirm the hypothesis. Therefore ICR will conduct a laboratory study to assess repellency of these test articles against *Culex quinquefasciatus* mosquitoes." (p. 12)

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

"It is well documented that Culex sp. Are known as primary vectors of West Nile virus (WNV) in the wild. . . . Based on this reasoning, the EPA has recommended that laboratory data with uninfected mosquitoes can be used to support the addition of WNV product label claims. Therefore, this laboratory cage study (utilizing disease free mosquitoes) is being specifically conducted to support additional label claims that the above registered products repel mosquitoes that may transmit West Nile virus." (p. 12)

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

EPA will consider the study in determining 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?

Previous product-specific field efficacy data to support the registrations of the two test products did not address efficacy against *Culex* sp. The proposed test materials have not previously been tested for efficacy against mosquitoes in this genus.

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

"There are currently no viable alternatives to . . . human studies for determination of the performance characteristics of insect repellents. . . . EPA requires that efficacy data collected from human studies be submitted for EPA review in order to obtain approval for an insect repellent registration. The data must substantiate the public health protection claims made on the product's labeling." (p. 13)

"According to the EPA OPPTS Guideline No. 810.3700 "Product Performance of Skin-Applied Repellents of Insects and Other Arthropods" there exists no alternative to evaluating topical repellents on human subjects; therefore, field or laboratory testing of repellents is necessary." (p. 14)

"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." (p. 17)

2. Study Design

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

"The objective of the study is to determine the mean protection time from bites provided by the test articles under laboratory conditions to confirm the hypothesis. Therefore ICR

will conduct a laboratory study to assess repellency of these test articles against *Culex quinquefasciatus* mosquitoes." (p. 12)

"Hypothesis: The repellent samples are expected to provide 8 hours of personal protection from *Culex quinquefasciatus* mosquitoes, a West Nile virus vectors, in the laboratory." (p. 12)

(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 repellent 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 control subject, 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. 24)

The proposed sample size will 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?

"One untreated arm of the control subject will serve as a negative control. The control will be selected from the total pool of test subjects by drawing a name. The control landing rates will serve to establish the aggressiveness of the mosquitoes. No comparison will be made between the control landing rate and the treated subjects.

"The control test subject will expose his/her untreated forearm in the test cages to confirm the aggressiveness of the mosquitoes prior to each exposure period. The acceptable level of aggressiveness will be at least 5 landings in 60 seconds. If fewer than 5 mosquitoes land in seconds, a new group of 100 mosquitoes will be released into all of the cages. Mosquitoes will not be allowed to bite. The control will vigorously shake his arm as mosquitoes land, to prevent these landings from turning

into bites. ICR staff will count the landings as they occur." (p. 19, as amended by Amendment #6.)[3]

"A positive control is intentionally excluded from the proposed study protocol for several reasons. . . . Putting additional subjects at risk, however minimal, to include a positive control group is not necessary." (pp. 19-20)

"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." (p. 26)

"The control text subject will be randomly selected by ~~flipping a coin~~ drawing a name." (p. 27, as amended by Amendment #8.)[3]

"*Determination of Attractancy to Mosquitoes*. Test subjects will then be taken to the insectary. They will then place their right forearm into their test cage and the number of mosquitoes landing on their arms will be counted. The required landings will be at least 5 mosquitoes in 60 seconds to qualify a subject as being attractive to the mosquitoes. Volunteers 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 . . . that subject may be replaced." (p. 27)

"The aggressiveness of the caged mosquitoes during the test day will be determined from the landing rate on the control's arm before each test exposure. Once the landing rate has been confirmed (5 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 mosquitoes land in 60 seconds, a new group of 100 mosquitoes will be released into all of the cages." (p. 28)

Qualification of all treated subjects by establishing their attractiveness to the colony of test mosquitoes used for this study is appropriate, although using both arms up to twice each may be excessive. Use of an untreated control to confirm continued aggressiveness of test mosquitoes throughout testing is appropriate for the study design. Omission of positive controls is acceptable for the study design. No direct comparisons of treated and untreated subjects are contemplated in the statistical analysis plan.

There is inconsistency in the descriptions on pages 19, 26, and 27 of how the control subject will be selected; all three references should be made consistent. The meaning of the reference to the "total pool of test subjects" in the first quoted passage above is unclear: it could refer either to the entire ICR database or to the group of subjects enrolled for this study. This should be clarified.

[3] In these and similar cases the quotation shows both the original text and the effect of the amendment, using redline/strikeout conventions.

(c) How is the study blinded?

"This is a subject-blinded study. . . . 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. . . . The test articles will be coded as 'A' and 'B'. 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. . . ." (pp. 25-26)

"The 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. 27)

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

"One untreated arm of the control subject will serve as a negative control. The control will be selected from the total pool of test subjects by drawing a name." (p. 19)

"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." (p. 26)

"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." (pp. 25-26)

(e) Can the data be statistically analyzed?

Yes.

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

"The purpose of this study is to examine the effective duration of an insect repellent. Ideally, it is expected that there will be no significant breakdown in efficacy of the product over a 8 hour interval. Given the small sample size (N = 10) and the dichotomous nature of the data (effective vs. non-effective), nonparametric statistics will be used to analyze the data. Data will be analyzed using SPSS for Windows version 12.

"Subjects will be evaluated each half hour over the 8 hour window of the study to determine whether or not the product continued to prevent insect bites. For each 30 minute assessment interval, the proportion of subjects not having insect bites will be identified. A basic degradation curve can then be plotted. These data will then be

subject to a Cochran Q test, which is particularly useful for measuring changes in frequencies (proportions) across time. A significant effect would indicate that there was a systematic degradation in the product's efficacy over the 8 hour testing interval. If such an effect is found with the Q test, then a series of 2 (baseline vs. assessment interval) X 2 (protected vs. non-protected) cross-tabulations will be created and the resulting proportions will be analyzed using a Fischer's Exact Test (employing a 1-tailed alpha level) to determine the specific time point at which efficacy became significantly impaired.

"Data also to be collected from subjects will be the length of time before a significant number of bites were noted. These data will be aggregated and basic descriptive statistics determined (e.g., mean, standard deviation, confidence intervals). If this distribution is non-normal, appropriate transformations will be applied and statistics recalculated. In the case of negative skewness (which is expected), the data will be reflected and a logarithmic transformation will be employed. In the case of significantly skewed distributions, the median will be used as the measure of central tendency. Confidence intervals will be calculated on the basis of percentile ranks rather than standardized scores." (p. 29)

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

The proposed statistical measure for duration of repellency may be appropriate in the case that the data are not normally distributed. The protocol is unclear as to how the nonparametric analysis will be applied to determine protection time when compared to the discussion found in the paragraph on central tendency and descriptive statistics (p.29). The latter paragraph provides a calculation of confidence intervals based on percentile ranks but does not explain how these ranks might be used to determine protection time.

The discussion also does not explain how data will be handled from subjects who withdraw from testing before reaching either efficacy breakdown or the 8-hour time limit.

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

Yes. It should produce a data set similar to those 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 registered repellent products to the approved labeling of which the registrant wishes to add a claim of efficacy against "mosquitoes that may transmit West Nile virus." (p. 12)

Subjects will also be exposed for five of every 30 minutes during the efficacy trial to caged laboratory-bred and disease-free *Culex quinquefasciatus* mosquitoes. *Culex* sp. mosquitoes in the wild are known vectors of West Nile virus. (p. 12)

(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 converted to a volumetric dose by considering the specific gravity of the test formulations, will be used for all subjects. Each arm of each treated subject will be treated by an ICR technician with one of the two test repellents; exposure to the repellents will be continuous throughout the period of the test.

(c) What duration of exposure is proposed?

"Exposures to the mosquitoes will be repeated every 30 minutes until the formulation on any given forearm is determined to be no longer effective or until 8 hours have elapsed, whichever occurs first." (p. 28)

2.3 Endpoints and Measures

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

"ICR prefers to evaluate repellency based on protection from bites rather than landings while conducting laboratory studies. Disease transmitted by laboratory raised mosquitoes that have not been exposed to any arbovirus is not possible. Therefore there is no risk of disease transmission to any of the test subjects.

"In this study efficacy is defined as the Protection Time (PT). The PT is the time between the application of the repellent and the First Confirmed Bite (FCB). . . . The FCB is a bite which is followed by another bite within 30 minutes." (p. 14)

"The aggressiveness of the caged mosquitoes during the test day will be determined from the landing rate on the control's arm before each test exposure." (p. 28)

"The test data to be recorded will be bites. . . . Treated test subjects will expose their treated arms to the caged mosquitoes for 5 minutes at approximately 30 minute intervals. The test subjects will expose treated arms until the FCB . . . or until 8 hours have elapsed, whichever occurs first." (p. 28)

Landing pressure on the untreated control and FCB (First Confirmed Bite) on each treated arm are potentially appropriate endpoints, but it isn't explained why landings are appropriate to verify "aggressiveness of the caged mosquitoes" but bites are necessary to measure a failure of efficacy.

The data collection forms attached to the protocol (pp. 32-34) make no provision for recording the results of preliminary "attractancy" testing of subjects to be treated with repellent. The data collection sheet for the untreated control subject (p. 32) still calls for subject signature; this should be deleted.

(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. 20)

(c) What QA methods are proposed?

"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." (p. 30)

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

"Data also to be collected from subjects will be the length of time before a significant number of bites were noted. These data will be aggregated and basic descriptive statistics determined (e.g., mean, standard deviation, confidence intervals). . . . In the case of significantly skewed distributions, the median will be used as the measure of central tendency. Confidence intervals will be calculated on the basis of percentile ranks rather than standardized scores." (p. 29)

The discussion is this paragraph requires further clarification. It is unclear as to how these data and resulting evaluation will be applied to the determination of protection time.

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 to protect themselves against vectors of WNV. 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 developed a pool of male and female test subjects. The test subjects we recruit represent a diverse group including professionals such as working teachers, business owners and engineers, as well as students, housewives and others." (p. 18)

(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. Our test subjects need to be in good health to withstand the rigors of testing. We will accept individuals between the ages of 18 to 55. This age group represents a large portion of the population who through their diverse activities would both encounter mosquitoes and could have a need to use insect repellents." (p. 18)

Excluding children, adults over 55, pregnant or nursing women, non-English speakers, and those in poor health means the 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 criteria: "Age: 18-55; Literacy: Must be able to read, speak, and understand English. (Protocol p. 23) "Must be attractive to mosquitoes, as evidenced by previous being bitten. . . . Must wear proper protective clothing. . . . Must follow the requirements of the study as explained to them." (Protocol p. 24)

"You must be between 18 and 55 years of age and consider yourself to be in good health. You must be able to read, speak and understand English so you can follow directions." (CD p. 85) "You must be willing to provide your own transportation to the ICR lab. You must be available to participate in the study for its maximum duration of one day." (CD p. 86)

Exclusion criteria:

- Pregnant or breastfeeding
- Employee or relative of employee of ICR, Avon, or any interested party
- Known sensitivity to mosquito bites
- Known sensitivity to insect repellents or skin care products
- Smoking or drinking alcohol within 12 hours before or during the test
- Using scented products after midnight the night before or during the test (Protocol p. 24; CD pp. 85-86)

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. The rationale for requiring subjects to wear protective blue jeans and heavy socks for a laboratory cage test is not obvious.

The requirement (p. 24) that attractiveness to mosquitoes be established by having previously been bitten appears to be inconsistent with the proposal (p. 27) to qualify all potential subjects by directly testing them for attractiveness to the test mosquitoes.

Eligibility criteria are described differently in the protocol and in the Consent Document. Inconsistencies should be reconciled before the research goes forward. It would be appropriate to include all criteria worded positively under the heading of "inclusion criteria", and all criteria worded negatively under the heading of "exclusion criteria."

(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. 25) Employees and relatives of employees of ICR, the sponsor, or any other interested party are excluded as subjects. (p. 24)

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

No potential subjects from a vulnerable population are proposed.

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

"All subjects will sign "Informed Consent Statements" prior to acceptance as a study participant. The Informed Consent Document will be formally explained to all of 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~~ or by mailing ICDs prior

to the study, to try to eliminate any potential test subject not interested in the project." (Protocol p. 19, as amended by amendment #5.)[4]

"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. . . .

"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 fully 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." (Protocol p. 25)

"Prior to the test, we will discuss with you every line of the ICD. If you visit our Baltimore office, you may voluntarily sign the ICD at that time if you wish to be considered for participation in the study. If you do not want to visit our Baltimore office, we will mail the ICD to you, and fully discuss it with you via phone. You may subsequently sign the ICD but it must be in the presence of one of our study personnel. We will notify you within one week whether we have selected you for participation." (CD p. 86)

The description of the recruiting process must be expanded and clarified to satisfy the requirement of 40 CFR §26.1125(d) for "a description of the circumstances and methods proposed for presenting information to potential human subjects for the purpose of obtaining their informed consent." Differences between the three quoted descriptions of the recruiting process should be reconciled and the timing of the "visit to the Baltimore office" should be clarified before the research goes forward. The revised description of the process must make more careful distinctions among "potential subjects," "potential subjects who have shown interest in learning more," and enrolled "subjects," who have consented to participate in the research. To describe as "test subjects" people who have not signed a consent form—as is done repeatedly in the quoted passage from p. 19—is unacceptable.

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

Exclusion of employees and relatives of employees of ICR, the sponsor, or any other interested party safeguards potential subjects from coercion or undue influence.

[4] The quotation shows both the original text and the effect of the amendment, using redline/strikeout conventions.

3.3 Remuneration of Subjects

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

"The subjects will be paid $11/hour for a typical 9-hour test day, for a total payment of $99 for the day." (Protocol p. 19)

"We will pay you $99/day for an anticipated 9-hour work day. . . . 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 rate of $11 per hour." (CD p. 89)

(b) Is proposed remuneration so high as to be an undue inducement? No.

(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?

"Payment will be mailed to the subjects on the 15th or 30th of the month." (p. 19, 89)

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?

"The EPA "New Pesticide Fact Sheet" indicates that the toxicology data base for the active ingredient is complete and no additional studies are required." (p. 20)

"The inert ingredients in the test samples were selected because they are widely used in cosmetic and personal care formulations, and are non-sensitizers." (p. 21)

Prerequisite studies relevant to this research are studies of the acute toxicity of the two products tested. These studies were submitted at the time of product registration.

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

Risks of three kinds are identified: the risk of a reaction to the tested repellents, the risk of a reaction to mosquito bites or probes, and the risk of contracting a mosquito-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." (p. 20)

"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 low toxicity for acute inhalation toxicity and skin irritation. The EPA has classified it as mild toxicity for eye irritation. The Sponsor has selected the inert ingredients in the formulation because these inerts are widely used in cosmetic formulations, and have a long history of safe use." (CD, p. 89)

"The typical reaction to a bite from a mosquito can vary from person to person. Most people will experience a small area of redness, swelling and itching that usually goes away within 24 hours. In more sensitive individuals, the area of swelling and itching can be much larger and last for several days. In extremely rare cases, a serious reaction to a bite results in swelling of the throat, hives and wheezing. This condition (anaphylaxis) could be life-threatening and requires immediate medical attention." (Protocol p. 21)

"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. This could be life threatening." (CD p. 88)

"There is no risk for arthropod-borne diseases. The mosquitoes being used in this test . . . can carry the West Nile virus, St. Louis encephalitis, and both Western and Venezuelan equine encephalitis. This strain of mosquito has been laboratory colonized for many years and has not been exposed to outside blood sources. None of the mosquitoes used in this test will have had a blood meal prior to their introduction into the test cages. . . . Once a group of mosquitoes has been used in a study, it will not be re-used in another study. Therefore, transmission of a blood borne disease by these mosquitoes is not possible." (Protocol p. 22)

The possibility of contracting a mosquito-borne disease is not mentioned in the Consent Document. This omission is acceptable, because of the vanishingly low probability of such an event's occurrence.

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

No probability is estimated for the risks of reactions to the repellents or to mosquito bites. The probability of contracting a mosquito-borne disease is characterized as "minimal" (p. 13), and as zero elsewhere (p. 14, 22).

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. 24)
- Subjects "will be monitored throughout the study and prompt medical attention will be obtained if any adverse reaction is observed." (p. 21)
- Candidates "known to have severe reactions to mosquito bites" are excluded. (p. 22)
- "Once a confirmed bite occurs, the test subjects will stop exposing that arm to mosquitoes." (p. 28)
- Subjects will expose "only a small area (250 cm^2) of skin on each arm" for five minutes of every thirty during the test.
- Experienced technical personnel will be present at all times to assist.
- Testing is conducted with lab-reared, disease-free mosquitoes.
- Only one untreated control to confirm mosquito aggressiveness; no positive controls.
- Exposure of untreated control for no more than 1 min/half hour; exposed arm will be withdrawn from cage immediately following the fifth landing. "Mosquitoes will not be allowed to bite. The control will vigorously shake his arm as mosquitoes land, to prevent these landings from turning into bites." (p. 19, as amended by Amendment #6)[5]
- First Aid materials and First-Aid qualified staff will be available on-site.
- Prior notification of a local hospital.
- 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 835 mg repellent applied to 500 cm^2 skin[6]. The concentration of picaridin in the test materials is 10%; thus 835 mg product is equivalent to 83.5 mg picaridin. Because the ethanol in the formulations increases percutaneous absorption, this figure is adjusted by an "ethanol enhancement" factor of 2.26, yielding an adjusted dose of 189 mg, equivalent to 2.7 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—5000/2.7, or 1,852.

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[5] The quotation shows both the original text and the effect of the amendment, using redline/strikeout conventions.

[6] The standard dose rate is 1.67 mg/cm^2. Treated area is 250 cm^2 on each forearm, or 500 cm^2. Total dose of product for each subject is thus 1.67 x 500 = 835 mg.

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

"The test subjects will expose treated arms until the FCB (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) or until 8 hours have elapsed, whichever occurs first. . . . When the two bites have occurred as noted above, the test will terminate on that arm." (p. 28)

(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, St. Agnes Hospital, by either ICR staff or professional ambulance." (p. 22)

(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. 13)

(e) 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 principle investigator will contact all test subjects by telephone, two weeks after the conclusion of the study to enquire if they have experienced any adverse effects." (Protocol p. 23)

"The principal investigator will contact you by telephone, two weeks after the conclusion of the study to enquire if you have experienced any adverse effects. You should contact the P.I. if you experience any study-related adverse effects after this follow-up call." (CD p. 89)

(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." (Protocol p. 22)

"In the event that study related injury or illness should occur, test subjects would be instructed to seek medical attention through a health care provided, at ICR's expense. Test subjects would be instructed to submit study related bills to ICR. ICR will incur the cost of any study related bills." (Protocol p. 23)

"We will pay all of your medical bills for study-related illnesses and injuries." (CD p. 89)

5. Benefits

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

"While you will 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." (CD p. 89)

The results of this proposed research could NOT help bring a new repellent to the market. Both test repellents are already available in the market. This statement of benefit to subjects in the CD is misleading; no discussion of benefits to subjects appears in the protocol.

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

"While the sponsor gains the most direct benefit from the conduction of this study through knowledge gained on the performance of its repellent products, ICR and the sponsor also acknowledge that greater benefits exist to society at large. Insects continue to have a substantial impact on outdoor activities of many people. As the EPA registration requires efficacy data, the protocol in discussion is the only path toward development of alternative and perhaps more effective insect repellent products." (Protocol p. 23)

This discussion of the societal benefit of new insect repellents is irrelevant to this proposed research, which is intended to support modified label claims for two already-registered repellent products.

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

Assuming testing confirms the stated hypothesis, the only direct beneficiary of the research is likely to be the sponsor.

(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 in the form of increased sales of its registered products. Other societal benefits have not been characterized.

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, the risk of irritation from mosquito bites could be further reduced by treating landings and probes as evidence of failure of efficacy, in addition to bites. Excluding landings and probes as evidences of efficacy failure makes the study both riskier for the subjects and a less demanding test of product performance.

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 is entirely irrelevant to the knowledge likely to be gained from the research, which is designed to support additional label claims for already-registered repellents, not to bring alternative repellents to market.

Notwithstanding the weaknesses of the arguments concerning the expected benefit of this research, there is potential societal benefit in identifying registered repellents which are effective against *Culex* mosquitoes without exposing subjects to wild *Culex sp.*, which could vector WNV. 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 repellents of Culex mosquitoes.

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. 18)

EIRB is not listed as an accredited organization on the PHRP website (www.phrp.org). EIRB is not listed as an accredited organization on the AAHRPP website (www.aahrpp.org). AAHRPP does not identify organizations for which accreditation is pending.

(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.

(f) 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 EIRB, the EIRB's approval letter, and minutes of the EIRB discussion are provided.

Acceptable documentation of EIRB procedures has previously been provided directly to EPA.

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

"ICR, Inc., (ICR) policy complies with the final rule by adhering to 40 C.F.R. Part 26 Subparts K and L, when human volunteers are used. Thus ICR submits all necessary documentation to an independent institutional review board (IRB) for their review. The IRB will grant approval of the study protocol and the ICD if the rights and welfare of the participants are protected and the study will be carried out in an ethical manner." (pp. 17-18)

This passage correctly cites the applicable standards in 40 CFR Part 26 Subparts K and L. It inaccurately and unnecessarily describes the IRB's criteria for approval, which are specified at 40 CFR §26.1111.

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?

The Consent Document does not identify any benefits of the research, to the subjects or to others. It otherwise meets the requirements of 40 CFR §26.1116.

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

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~~ or by mailing ICDs prior to the study, to try to eliminate any potential test subject not interested in the project." (Protocol p. 19, as amended by Amendment #6)[7]

"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. . .

"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 fully 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." (Protocol p. 25)

"Prior to the test, we will discuss with you every line of the ICD. If you visit our Baltimore office, you may voluntarily sign the ICD at that time if you wish to be considered for participation in the study. If you do not want to visit our Baltimore office, we will mail the ICD to you, and fully discuss it with you via phone. You may subsequently sign the ICD but it must be in the presence of one of our study personnel. We will notify you within one week whether we have selected you for participation." (CD p. 86)

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

[7] The quotation shows both the original text and the effect of the amendment, using redline/strikeout conventions.

Candidates are offered opportunities to decide not to participate; participants are offered opportunities to withdraw. Exclusion factors rule out participation by employees or relatives of employees of ICR, the sponsor, or any other interested party. Recruitment of alternate subjects makes it less likely that subjects will 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?

"The test subjects' first and last initial and their dedicated identity number only may be referenced. . . . Essex Institutional Review Board has the right to review their records." (Protocol p. 29)

"We will reference only your first and last initials and your dedicated identity number in the report. However, . . . the sponsor, personnel associated with the study, a regulatory agency such as the Environmental Protection Agency (EPA), and the Essex Institutional Review Board (EIRB) have a right to review your records." (CD p. 90)

The data collection form for control data (p. 32) inappropriately calls for subject signature.

"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. 26)

Recruitment of alternate subjects provides an opportunity for discrete withdrawal without explanation.

(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 Consent Document.

(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. (CD p. 89).

§ 26.1111 Criteria for IRB approval of research
ICR Protocol No: G0590607001A117 (Version of 8/8/2007)

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.	N	Risks can be further reduced by treating landings as the endpoint of concern
(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	Risks to subjects are very low, and notwithstanding poor characterization of societal benefits, offset by potential societal benefit of identifying registered repellents effective against *Culex* mosquitoes.
(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: G0590607001A117 (Version of 8/8/2007)

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 process described in protocol 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 CD 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. 85
	(2) A description of any reasonably foreseeable risks or discomforts to the subject	OK	pp. 88-89
	(3) A description of any benefits to the subject or to others which may reasonably be expected from the research	N	p. 89. Characterization of benefits is inadequate
	(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject	OK	p. 90
	(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained	OK	p. 90
	(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	p. 89. Research does not involve more than minimal risk, but does provide for compensation and medical treatment
	(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. 90
	(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. 90
(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. 89
	(3) Any additional costs to the subject that may result from participation in the research	OK	p. 89
	(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. 86
(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	Identity of A.I. p. 89 Function p. 85

§26.1117 Documentation of informed consent
ICR Protocol No: G0590607001A117 (Version of 8/8/2007)

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. 85-90
(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 consent form meets requirements of §26.1116; procedure described in protocol 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 Prior submission of proposed human research for EPA review
ICR Protocol No: G0590607001A117:Aug 8, 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
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	10-34, 36-41, 73-80 85-90
	(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	69-72 Full EIRB met 7/30/07; conditional approval unanimous; no controverted issues. Final approval 8/2/07 by Chair.
	(3) Records of continuing review activities.	n/a	n/a for protocols
	(4) Copies of all correspondence between the IRB and the investigators.	Y	See §1125(e) below
	(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	92-94; weak on rep capacity and experience; no description of each member's chief anticipated contributions
	(6) Written procedures for the IRB in the same detail as described in §26.1108(a) and §26.1108(b).	N	On file at EPA
	(7) Statements of significant new findings provided to subjects, as required by §26.1116(b)(5).	n/a	n/a for protocols
The following Information, to the extent not already included:	§1125(a) a discussion of: (1) The potential risks to human subjects	Y	20-22
	§1125(a) a discussion of: (2) The measures proposed to minimize risks to the human subjects;	Y	20-22
	§1125(a) a discussion of: (3) The nature and magnitude of all expected benefits of such research, and to whom they would accrue	N	p. 23 discussion irrelevant; covers only bens of new prods
	§1125(a) a discussion of: (4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and	Y	12-14
	§1125(a) a discussion of: (5) The balance of risks and benefits of the proposed research.	N	
	§1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB.	Y	Consent Documents
	§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.	Y	18, 25 No ads or flyers
	§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.	N	
	§1125(e): All correspondence between the IRB and the investigators or sponsors.	Y	7, 9, 43-67, 69-82
	§1125(f): Official notification to the sponsor or investigator . . . that research involving human subjects has been reviewed and approved by an IRB.	Y	82-84