UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C., 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

March 7, 2008

MEMORANDUM:

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

FROM: John M. Carley
Human Research Ethics Review Officer

Kevin Sweeney,
Science Reviewer

TO: Marion Johnson, Chief
Insecticide Branch, RD

REF: Gaynor, W. (2008) Evaluation of the Efficacy of KBR 3023 (Picaridin; Icaridin)-Based Personal Insect Repellents (20% Cream and 20% Spray) Against Stable Flies in the Laboratory. Unpublished protocol dated February 1, 2008, with supporting materials, prepared by ICR, Inc., under Protocol No. G4330108001A382 and Sponsor Project No. 0108-433-0161. 343 p.

We have reviewed the referenced protocol for a laboratory test of stable fly 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 balance of risks and benefits of the proposed research, as required by 40 CFR §26.1125(a)(5). Although this omission must be corrected before going forward with the research, it does not compromise our ability to review the proposal.

- Written procedures for the IRB in the same detail as described in §26.1108(a) and §26.1108(b). The complete procedures manual for Essex IRB was previously submitted directly to EPA.

In addition to the final approved protocol itself (pp. 8-36[1], with appendices I-VI pp. 37-70) the submitted package included the following supporting documents—all considered in this review:

- Statement of No Confidentiality Claims (p. 2)
- Statement of GLP Compliance (p. 3)
- Initial transmittal of protocol to EIRB (p. 110)
- Informed Consent Documents (CDs)
    - As initially submitted to the EIRB (pp. 144-168; 173-191)
    - As revised 2/1/08 and resubmitted to the EIRB (pp. 289-302; 323-342)
    - As approved by EIRB 2/4/08 (pp. 884-103)
- Site Application Letter as submitted to the EIRB (pp. 214-222)
- MSDSs for test materials (pp. 192-210)
- Indemnification Agreements Lanxness/EIRB (p. 212) and Lanxness/ICR (p. 213)
- "Investigator Attestation of Qualifications" (p. 224)
- "Investigator Conflict of Interest Declaration" (p. 225)
- EIRB letter of 1/28/08 reporting conditional approval and calling for many non-substantive changes (pp. 227-234)
- EIRB minutes of 1/28/08 meeting (pp. 235-244)
- Amendment #1 of 2/1/08 with attachments responsive to EIRB comments (pp. 246-342)
- EIRB approval letter of 2/5/08 (p. 7)
- EIRB "Statement of Compliance" (p. 107)

The initial transmittal of the protocol to EIRB (p. 110) cites in the list of attachments CVs for three sub-investigators (Charles Cornell, Gloria Stevens, and Fouad Zgidou), and says that CVs for all other investigators are on file at EIRB. No CVs are included in the submitted supporting documentation. The Site Application Letter (p. 217) asserts that all "CVs are on file at Essex IRB."

[1] Many pages bear more than one page number. All page references in this review are to "page N of 343" entries.

B. Summary Assessment of Ethical Aspects of the Proposed Research

The ethical aspects of the proposed protocol are summarized below. 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 conditionally registered topical picaridin-based repellents against stable flies in the laboratory for up to 10 hours. EPA requires product-specific efficacy data to support label claims of repellent efficacy against biting flies. Although these materials have previously been tested in the field for efficacy against other insects, they have not previously been tested against stable flies or other biting flies.

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." The pool is also noted to include only white candidates, unlike the surrounding community, which is reported to include roughly 20% African-Americans and 5% other races. An effort to recruit African-Americans for this study is promised, but no details are provided about how that might be done.

   Children, adults over 70, 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 stable flies.

   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 preliminary dose-termination test would be paid $99. Those who complete the repellent-phase testing would be paid $134.

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

   - Risks of reaction to the repellents are reduced by excluding candidates with known sensitivity to repellents or skin care products and by monitoring subjects closely for reactions.

     The estimated total dose of picaridin for each treated subject is about 377 mg, roughly equivalent to 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, even in ethanol, and the inert ingredients other than ethanol are not expected 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.

- Risks of stable fly bites are reduced by excluding candidates known to be "unduly sensitive" to them, 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 by attempting to remove landing stable flies before they bite.

- The risk of contracting an arthropod-borne disease is characterized as zero, because the stable flies are laboratory-reared and disease-free, and will not have had a blood meal.

- 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 correctly states that participating in the research will be of no benefit to subjects. The protocol identifies the sponsor as the greatest beneficiary of the research, and asserts potential indirect benefits to society from development of "more effective, safer and 'pleasant-to-use' repellent products."

   Assuming the testing shows good efficacy and supports continued regulatory approval of the products with 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 picaridin-based repellent which has been shown to be effective against stable flies.

5. **Risk/Benefit Balance:** Although the risk of a reaction to stable fly bites could, in principle, be further reduced by interpreting landings as evidence of failure of efficacy, rather than only bites, the protocol includes a persuasive rationale for using bites as the endpoint event.

   There are no direct benefits of this research to the subjects, so its 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, asserting only the benefits of developing alternative repellents. Since these test materials are already conditionally registered and in the market, such benefits cannot result from this research.

   The protocol does not discuss the balance of risks to subjects and benefits to others. Notwithstanding the weaknesses of the discussion of the expected benefit of this research, there is potential societal benefit in identifying registered repellents which are effective against stable flies. Risks to subjects have been effectively minimized, and 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 January 28, 2008, at which this protocol was discussed. They do not explain the basis for requiring changes in the protocol and consent forms, but call for some 91 changes, most of which were corrections of punctuation, spelling, or typographic format. One requested substantive change would have introduced a frank error. Two other passages inserted by EIRB in each consent form are inappropriate for the proposed research. The amended protocol of February 1 responded to all EIRB requests for changes with two exceptions: the erroneous "correction" to the reference to exceeding the MOE target was not implemented, and another EIRB comment called for a change to a sentence which did not occur in the location cited.

7. **Informed Consent:** The protocol as submitted includes numerous versions of the consent forms both as submitted to the EIRB and as revised and approved. Two consent forms are involved—one covering the dose-determination phase of the study, and the other covering the repellent phase. Subjects who participate in both phases would sign both consent forms. In addition, the consent forms are provided both as Appendices II and III to each version of the protocol and as free-standing documents. The final approved consent forms satisfy the applicable requirements of 40 CFR §26.1116 and §26.1117.

   The processes of recruiting and informing candidates and seeking their consent are described acceptably in the protocol. Potential subjects are initially contacted by telephone from a database of former subjects of repellency tests. This telephone interview will follow a script incorporated as Appendix VI to the protocol, and approved by the EIRB. Candidates 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.

8. **Respect for Subjects:** Methods proposed for managing information about prospective and enrolled subjects will generally protect their privacy from compromise.

> "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 deficiency should be corrected before the research is initiated:

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

When this deficiency has 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 repellent efficacy of two conditionally registered products containing picaridin against the stable fly, *Stomoxys calcitrans* L., in the laboratory. The study would establish the mean and median times to the first confirmed bite for each formulation to support label claims of repellency against stable flies. These objectives can be met by the study as proposed.

1. **Study design:** The protocol has two objectives: to test the repellent efficacy of the conditionally registered picaridin formulations against stable flies and to establish a typical consumer dose for each product, to be used as the standard dose in the efficacy phase. In the dosimetry phase, the test dose will be determined before repellency testing is conducted. In the repellency phase, ICR will apply the products at the dose resulting from the dosimetry phase. This treatment regime is adequate to produce reliable data. Repellency evaluations will be based on the First Confirmed Bite (FCB) test. This procedure will require both of the subject's forearms to be exposed in a cage containing 25 adult stable flies for 5 minutes every 30 minutes for 10 hours, or until the first confirmed bite occurs on both arms, whichever comes first. This design is reasonable and scientifically sound for testing the repellent claim of eight hours. However, a positive control treatment is not proposed as part of the protocol's study design. As there are few biting fly studies on picaridin products, a positive control will improve the study design and aid in the validation of results. Therefore, a positive control treatment is recommended.

2. **Statistical Design:** The statistical design is adequate and acceptable. The study director makes a concise but sound argument for the sample size justification in this experiment as well as for the duration of the repellency phase needed to test the eight hour claim. It should be noted that the data reviewed and analyzed by Rutledge and Gupta (1999) were mosquito repellency studies. After reviewing their own database of stable fly repellent studies from 1990-99, ICR concluded that a sample size as small as seven subjects could be used. However, they opted for the more conservative approach to reduce uncertainty and insure statistical reliability by using a sample size of 12. If the repellent lasts for 10 hours on all subjects, the researchers will conclude that the product was effective for eight hours ±2 hours.

   The table presented on page 35 describes protection times up to eight hours and their associated standard deviations around a 95% confidence interval, but only for sample sizes up to seven subjects. This table will not be used in the analysis, and was provided to support the investigators' sample size argument. The results of Kaplan-Meier analysis as presented from SPSS v.1.6 software will be used to determine protection times.

3. **How and to what will human subjects be exposed?** Each test formulation will be applied to one forearm of each subject. The amount of each product to be applied during the test phase will be based on the results of a dosimetry study that is designed to establish the typical consumer dose for each repellent product. The repellent will remain in place for up to 10 hours. Subjects will also be exposed to landings and bites by caged disease-free laboratory-reared stable flies. This approach is acceptable.

4. **Endpoints and Measures:** The First Confirmed Bite test will be used to evaluate repellency in this study. A stable fly will ingest blood from the test subject when the repellent fails to protect the exposed skin. A second bite must follow the first bite within the five minute exposure period or 30 minutes later in the next (consecutive) exposure period for the repellent to fail on that test subject's forearm. Stable fly host seeking and

biting behavior differs from that of mosquitoes. As these flies commonly land without biting, only to land again where they may or may not bite, the use of a bite instead of a landing as a measurable endpoint for evaluating repellency is definitive, hence a more accurate measure of repellent failure. The only perceived drawback to this approach is that the same fly might bite a subject twice, leading to repellent failure. However, since this phenomenon can occur with similar frequency in the field, this source of variation is acceptable. An ICR analysis of 9 stable fly tests conducted in their laboratory from 1990 to 1999 indicated that use of landings would significantly underestimate protection time when compared to bites.

The mean complete protection time will be used to report repellency results. Expressing repellency in this matter is supported by the science and regulatory literature and linked to the basis for the statistical power of this experiment.

E. Compliance with applicable Scientific standards

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

- Scientific objective and explicit hypothesis
- Methods, materials and 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 and statistical power
- Statistical methods and data analysis
- Rationale for use of one untreated subject to monitor aggressiveness of test mosquitoes.

Addition of a concurrent positive control treatment is recommended, preferably a product containing at least 20% DEET that is similar in formulation type and composition to the picaridin products to be tested. One forearm of each subject in the repellent phase should be treated with the picaridin product and the other with the positive control. We recommend the same subjects be used to test the 20% cream and the 20% spray. This may require the test to continue for more than one day to accommodate the necessary replications.

Attachments:

1. Summary Review of ICR Protocol G4330108001A382 dated 2/1/08
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 G4330108001A382

Title: Gaynor, W. (2008) Evaluation of the Efficacy of KBR 3023 (Picaridin; Icaridin)- Based Personal Insect Repellents (20% Cream and 20% Spray) Against Stable Flies in the Laboratory. Unpublished protocol dated February 1, 2008, with supporting materials, prepared by ICR, Inc., under Protocol No. G4330108001A382 and Sponsor Project No. 0108-433-0161. 343 p.

Date: 1 February 2008

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1. Societal Value of Proposed Research

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

"The objective of the study is to determine the mean protection time from bites by stable flies provided by the test articles under laboratory conditions to confirm the hypothesis." (p. 11)

"Hypothesis: Two repellent products . . . are expected to provided 8 hours or greater than 8 hours of personal protection from stable flies . . . in a laboratory test." (p. 11)

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

"No testing of 20% KBR 3023 products has been conducted against biting flies in the US or Europe. . . . Stable flies can transmit animal-related diseases, but very rarely transmit any diseases which afflict people. The pest status of these flies . . . is almost entirely due to their painful bite and annoyance. . . . The data generated from the study will provide consumers with an alternative and effective choice of repellent." (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?

Neither the proposed test materials nor any other repellents with this active ingredient at this concentration have previously been tested for efficacy against biting flies. (p. 12)

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

"Human subjects are required for this study because there are no satisfactory substitute models for testing insect repellents." (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 of the study is to determine the mean protection time from bites by stable flies provided by the test articles under laboratory conditions to confirm the hypothesis." (p. 11)

"Hypothesis: Two repellent products . . . are expected to provided 8 hours or greater than 8 hours of personal protection from stable flies . . . in a laboratory test." (p. 11)

(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 [discussion draft] EPA Guideline . . . currently on EPA's website recommends 10 test subjects to document a protection time greater than 5 hours. Because of the high cost of doing repellent studies and the need to avoid unnecessary exposure to subjects, it is prudent to ensure data is collected from the minimum acceptable number of subjects. Therefore the target number of test subjects in the study is twelve, which includes two additional subjects in case of drop outs or ones failing to meet an exclusion or inclusion criterion on the day of the test." (p. 29)

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

"The proposed study will use stable flies as the test organism, not mosquitoes. Stable fly behavior differs from that of mosquitoes; a meta-analysis for the former species is needed for a confident prediction of the sample size needed for a reliable estimate of protection time. ICR is unaware of any such study. We analyzed our own data base consisting of 9 stable fly repellent studies conducted between [1990] and 1999 in which the numbers of subjects ranged from 2 to 10. Our consulting statistician is of the opinion that the data are inadequate for deriving a reliable power estimate table, especially as many of the protection times were left (<0.5 hours) or right (>8 hours) censored. When these data had been excluded, the remaining data did not show survival time being significantly linked to standard deviation. With these caveats and following the procedures outlined by Rutledge and Gupta (1999), he derived the table shown below for 95% confidence levels, two-tailed with a 2-hour confidence interval.

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

"The table indicates that a sample size of seven subjects would be adequate. In view of the uncertainties noted above relating to this table, we have chosen to run this study with twelve subjects in an effort to minimize the risk of interpreting repellent protection from a too-small data set." (pp. 34-35)

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

"One subject will be selected to be the negative control . . . . by a drawing of numbers. One untreated arm of the control subject will be used to establish the

aggressiveness of each cage of 25 stable flies. . . . If fewer than two stable flies land in 60 seconds in any of the six test cages, all stable flies will be vacuumed from all six cages and a new group of twenty-five stable flies will be released into all six cages." (p. 25)

"EPA is not requiring positive controls. . . . A positive control group would not confirm the stable fly repellency of the test product nor would it help in determining a reliable protection period for these products . . . . Putting additional subjects at risk, however minimal, would be unethical." (p. 25)

However, when the efficacy database for picaridin was first developed, the study directors used DEET formulations of equal concentration and similar composition as a positive control in order to aid in the validation of test results.

"*Determination of Attractancy to Stable Flies*. Test subjects will be checked for their attractiveness to stable flies. Subjects will place their right forearm into their cage and the number of flies landing on their arms will be counted. The required landings will be at least 2 stable flies in 60 seconds to qualify a subject as being attractive to the flies. Volunteer will repeat the qualifying exposure as above using the left arm. The procedure will be repeated if the subject fails to qualify. If a subject again fails to qualify after repeated exposures, that subject may be dropped from the study." (p. 31)

Qualification of all treated subjects by establishing their attractiveness to the colony of test flies 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 flies 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.

(c) How is the study blinded?

"Each test subject will have one arm treated with the cream product and the other arm will be treated with the spray product. ICR staff will know the identity of the treatments, but the test subjects will not." (p. 29)

"The test articles will be coded as "A" (cream) and "B" (spray). . . . The study director and members of the ICR staff will know the actual test articles, but will refrain from such identifications in the presence of test subjects. It should be noted however that the different appearance and texture of the cream and the spray will probably be apparent to the subjects." (p. 30)

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

"One subject will be selected to be the negative control . . . . by a drawing of numbers." (p. 25)

"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. 30)

"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?

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

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

"In the event that *more* than two subjects drop out during the study, final estimates of protection time will be made that are consistent with the power parameters stated above." (p. 35)

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

Yes.

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

Yes. Based on the approach developed by Rutledge and Gupta (1999) and ICR's analysis of their own stable fly studies from 1990-99, the suggested sample size is 7 subjects. However, ICR proposes to use 12 subjects in this experiment to improve statistical reliability, especially in the event of subject drop-outs. This study should produce a similar data set 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 products (20% formulations of All-family Insect Repellent Spray and All-Family Insect Repellent Cream) are conditionally registered by EPA pending conduct of new efficacy data including stable flies." (p. 12)

Subjects will also be exposed for five of every 30 minutes during the efficacy trial to caged laboratory-bred and disease-free stable flies—*Stomoxys calcitrans L.*—a noxious pest. (p. 15)

"Groups of twenty-five adult, mixed sex, 3-10 day old stable flies will be aspirated from stock cages and released into each cage for each 5- minute exposure period. These test stable flies will have been fed 10% sucrose rather than their normal diet of citrated bovine blood. They will have had no sucrose for twenty-four hours prior to the study and they will have not have received a blood meal." (p. 16)

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

The proposed research includes a "dose determination" phase in which twelve subjects will apply each of the two test materials to each of their forearms three times. The grand mean of subject mean dose rates for each test product will then be used as a standardized "typical consumer dose" in the repellent phase. (pp. 24-25)

"The test articles will be applied to the test subjects using a syringe (minus needle), rubbed on by hand by an ICR staffer using their surgically-gloved hands. If the cream repellent is too viscous to be applied with a syringe, it will be applied with a cotton-tipped applicator stick. . . . The spray . . . will be dispensed into a 250 ml beaker after which it will be applied by syringe (minus needle). Application of the spray will differ from the manner in which it will be used by consumers or in the dose determination phase of the study. Application by syringe is, however, required to allow accurate measurement for equal treatment." (p. 31)

"Subjects will be treated in pairs. Both members of a pair will be treated with the cream and then with the spray. . . . The time when the application of the spray treatment begins. . . will represent the starting time used for calculation of the protection times." (pp. 31-32)

(c) What duration of exposure is proposed?

"The test subjects will expose their treated forearms to the stable flies for 5 minutes. . . . Exposures to the stable flies will be repeated every 30 minutes until the treatment on any given forearm is determined to be no longer effective or until 10 hours have elapsed, whichever occurs first." (p. 32)

2.3 Endpoints and Measures

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

"Required landings will be at least two stable flies in 60 seconds to qualify a subject as being attractive to the flies." (p. 31)

"The aggressiveness of the caged stable flies prior to each exposure period will be determined from the landing rate on the control's arm before each test exposure." (p. 32)

"The test subjects will continue to expose their treated arms to stable flies until the FCB (First Confirmed bite) or until 10 hours have elapsed, whichever occurs first. The FCB occurs when two bites occur on the same arm in the same exposure period, or one bite occurs in each of two consecutive exposure periods (the first bite being the confirmed bite) A bite is defined as a stable fly penetrating the skin with its proboscis and taking blood into its abdomen. When the two bites have occurred as noted above, the test will terminate on that arm." (p. 33)

"The repellent will be considered degraded if either of these two conditions is met: a) two stable fly bites are noticed in a single 5 minute observation period; or, b) a single bite in two adjacent observation periods is noted." (p. 29)

"Their arms will be exposed to live stable flies for five minutes. If two bites are noted in this time period, the case will be considered a 'bite'." (p. 29)

> This passage introduces ambiguity about the meaning of 'bite'. It appears to define a 'confirmed bite' as simply a 'bite', equating 'two bites' to 'a bite'. If the word 'confirmed' were inserted immediate before the last occurrence of 'bite', this passage would make sense.

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

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

therefore will greatly increase the chances that two different flies will be involved in the determination that the repellent product has lost its repellency (broken down).

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

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

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

"v) Stable flies often land long before they bite. A conservative analysis of 9 stable fly tests conducted by ICR from 1990 to 1999 revealed that the time difference between first confirmed landing and first confirmed bite ranged from 0 to 7.5 hours with a mean of 2.6 hours. Therefore ladings would seriously underestimate the protection time for the test products." (pp. 32-33)

Landings to test pressure on the untreated control and FCB (First Confirmed Bite) on each treated arm are appropriate endpoints.

(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

(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. 35)

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

"From the KM analysis we will take the mean and median survival times along with its 95% confidence interval as the final result of this study. In the event that all subjects right censor . . . we will conclude with 95% confidence, that the product can provide protection for up to 8 hours, ± 2 hours." (p. 35)

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 stable flies or other biting flies. 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 retired teachers, business owners, contractors, engineers, as well as students, homemakers and others." (p. 21)

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

"ICR's current pool of potential subjects are all white. Afro-Americans and North Africans have participated in previous studies. For the proposed stable fly test, ICR will look for recruits from the Afro-American community, as well as from the white majority population to correct this slight imbalance." (p. 20)

"ICR's list of potential subjects is as representative of potential repellent users as ICR is able to make it in terms of both practical and ethical considerations. ICR test subjects need to be in good health to withstand the rigors of the specific test. In the case of this laboratory test, the rigors will be very minor – boredom is likely to be the main one. ICR will accept individuals between the ages of 18 and 70. This age group represents a large portion of the US population who would encounter stable flies and have a need to use insect repellents." (p. 21)

"ICR will select individuals from its database of candidate test subjects. This will be accomplished by drawing numbers that correspond to the candidate subjects. ICR will attempt to select even numbers of male and female test subject (6 female and 6 male in this test) to eliminate any gender bias in this test. The reason for this is that gender has been shown to affect attractiveness of the subjects to mosquitoes and the same may be true of stable flies." (pp. 21-22)

Excluding children, adults over 70, 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:

"Male or Female; Age: 18-70; Literacy: Must be able to read, speak, and understand English. . . .Must be attractive to stable flies, as evidenced by previously being bitten." (p. 20)

"You must be at least 18 and not over 70. . . . You must be able to read, speak and understand English. You must be attractive to stable flies, as evidenced by at least 2 landings of caged stable flies on your untreated forearm within one minute. . . . You must agree to follow the directions of the Principal Investigator, . . . not to use tobacco, alcohol, or any scented cosmetic products after 8 p.m. the night before study, and on the day of the study until it is concluded, [and] to wear proper protective clothing on the day of the study." (pp. 94-95)

"For the repellent study only, you must be attractive to stable flies. We must verify this in the lab by inserting your untreated forearm into a cage of stable flies to see if at least 2 stable flies land within one minute." (p. 104)

Exclusion criteria:

- Pregnant or breastfeeding
- Employee or relative of employee of ICR, Lanxness, or any interested party
- Known sensitivity to stable fly bites, 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 (pp. 20, 85, 94, 104)

The applicability of the exclusion factor concerning sensitivity to insect bites is unclear. The protocol (p. 20) excludes those "known to be unduly sensitive to stable fly bites", but explains "this is not an exclusion from the dose-determination phase of the study." The consent form for the dose-determination phase (p. 85) excludes those with "known sensitivity to insect bites/stings." The consent form for the repellent phase (p. 94) excludes those with "known sensitivity to stable fly bites." The recruiting script (p. 104) states: "For the repellency test only, you cannot participate if you are sensitive to stable fly bites."

The requirement (p. 20) that attractiveness to stable flies be established by having previously been bitten is inconsistent with the proposal (p. 31) to qualify all potential subjects by directly testing them for attractiveness to stable flies. The recruiting script (p. 104) and repellent-phase consent form (p. 94) both describe the required "attractancy" testing and do not mention previously being bitten. The consent form for the dose-determination phase is silent with respect to this criterion.

These minor inconsistencies should be reconciled before the research goes forward.

(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. 22) Employees and relatives of employees of ICR, the sponsor, or any other interested party are excluded as subjects. (p. 21)

(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 candidates will review and sign an Informed Consent Document ('ICD') prior to acceptance as study subjects. The ICD will be formally explained to all candidates before the study is scheduled to begin. A candidate may visit ICR to review and sign the ICD or the ICD can be mailed to the candidate for their review. If mailed, the study director will phone the candidate to answer any questions regarding the ICD. If any candidate refuses to sign after learning the details of the document, they will not be allowed to participate in the study. After the ICD is fully described to the candidate, he or she may then sign the ICD in the presence of an ICR staff and a copy of the ICD will be made and returned to the candidate. He or she will then be notified within one week if they have been enrolled as a subject in the study." (p. 22)

"When a repellent study is planned, ICR will contact candidate subjects in its data base by telephone and briefly discuss the study. Any study specific inclusion/ exclusion requirements will also be mentioned at this time.

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

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

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

visit ICR's office prior to the study date, they must sign the ICD on the study day before taking part in the study.

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

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

"Each female candidate will be informed that if they sign the ICD and want to participate in the test, they will be required to perform an over the counter pregnancy test on the morning of the study. The test results will be confirmed by a female ICR employee and the study director. Once they have signed the ICD, each consenting test subject will be informed that they may drop out of the study at any time without penalty (except that they will lose some of their potential remuneration, based on the time they miss). Further, they may leave as soon as practical after early withdrawal from the test." (pp. 22-23)

(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.

3.3 Remuneration of Subjects

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

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

"For the repellent part of the study, the subjects will be paid $11/hour for the first 9 hours and $17.50 for each additional hour they spend on the day of the study. The study will last about 10 hours with approximately one hour of preparation time for a total of 11 hours. A total payment of $134 will be paid to each test subject for the day. If a subject drops out of the test at our request but they have complied with all of our requests, they will receive full payment. If the subject drops out of the test either at our request because they have not followed all of our directions, or they just choose to drop out, they will be compensated for their time up to that point at the rate of $11 per hour. " (p. 22)

"The day's [dose-determination] study may last up nine hours for all 12 test subjects, although your direct involvement should not last more than three hours." (p. 88) "We

will pay you $11/hour for the 9-hour duration of the study for a total payment of $99." (p. 89)

These two passages from the consent form for the dose-determination phase should be clarified, perhaps saying on p. 89 "for your direct involvement of about 3 hours you will be paid $99."

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

$99 for 3 hours is much higher than is typically paid by this and other laboratories for participation in this kind of research, and no explanation is offered for why subjects would be paid for a full 9-hour day. The quoted hourly rate is appropriate.

(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. 22)

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?

"In summary:
KBR 3023 has complete toxicology data supported by State-of-the–Art testing
Low acute toxicity
No irritant or sensitizing potential
No specific effects in rats or dogs in short-term and long-term studies NOAEL = 200 mg/kg (dermal); NOAEL = 308 mg/kg (oral)
Not mutagenic
Not tumorigenic
No effects on reproduction
No neurotoxicity
No photo-sensitisation or irritation
It is poorly absorbed through the human skin [1.66%]
Does not bio-accumulate and is rapidly excreted" (p. 66)

"The inert ingredients used in the two products have been used extensively in the cosmetic industry without adverse effects." (p. 13)

(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 stable fly bites, and the risk of contracting an arthropod-borne disease.

Risk of reaction to the repellents

"For registered products containing Picaridin®, the EPA risk assessment assumes that each application of insect repellent products is to a skin surface area of 4,538 cm^2 for adults. In the proposed test, the product will be applied once to the subjects on the test day over a surface area of only 500 cm^2 (*i.e.* 250 cm^2 on each forearm). Consequently, the test subjects in this study will only be exposed over an area of approximately 11 percent of that previously reviewed and approved by EPA for products with the same Picaridin® concentration. Further, the label directions of these registered products allow for up to two applications per day, while the efficacy study will employ only one (however the dose determination study will involve three or occasionally, four applications). A 100-fold margin of exposure (MOE) is considered to be the target for the determination of acceptable risk from systemic exposure. The MOE is based on the No Observed Adverse Effect Level (NOAEL) for systemic effects, the concentration of active ingredient in the formulation, frequency and rate of application, skin surface area and body weight, and dermal absorption. The MOE for the test subjects in this efficacy study will substantially exceed the minimum 100-fold target and is, therefore, considered acceptable under widely recognized scientific standards." (p. 27)

"You may have a reaction to the test repellents. . . . A reaction may include redness, irritation, burning, swelling, or a rash." (pp. 89, 99)

Risk of bites from stable flies

"The principal effect of a stable fly bite is a sharp but transient pain. In most cases, stable fly bites do not lead to the itching and localized swelling which are the typical aftermath of mosquito bites. A few people may experience a small area of redness, swelling and itching that usually goes away within 24 hours. In extremely rare cases, a serious reaction to a bite may result in swelling of the throat, hives and wheezing. This condition (anaphylaxis) could be life-threatening and requires immediate medical attention. All subjects known to have severe reactions to stable fly bites will be excluded from this study." (p. 27)

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

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

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

"Treated subjects will expose their forearms to stable flies for five minutes every half hour. Although they will not expose an arm further if they receive two bites on it in one exposure, or one bite in two consecutive exposure periods, they may receive more than two bites on each arm during the test. A bite which is not followed by another bite in the same or the next exposure will be disregarded. If you are a treated subject you will still need to receive at least two more bites on that arm to reach breakdown. The untreated control subject will be exposed to stable flies every half hour for up to one minute in each of six test cages. Although we will try to brush the landing stable flies off before they bite, the control subject is likely to be bitten by some of them. We will minimize the irritation from bites or probes you receive by making Caladryl® or Calamine® lotion or rubbing alcohol available at the study site for your use after the study is completed." (pp. 98-99)

Risks of arthropod-borne disease

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

"The stable flies being used in this test are not capable of transmitting diseases in the wild. This strain of stable fly has been laboratory colonized for many years and has not been exposed to outside blood sources while at ICR. None of the stable flies used in this test will have had a blood meal prior to their introduction into the test cages. Once a group of stable flies has been used in a study, it will not be re-used in another study. All stable flies used in the study will be destroyed either through freezing or carbon dioxide." (p. 28)

"The stable flies being used in this study will be laboratory-reared and disease-free, and they will never have had a human blood meal. There is therefore no risk of your contracting any stable fly-borne disease as a result of participation in this study." (p. 100)

(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 stable fly bites. The probability of contracting a stable fly-borne disease is characterized as zero.

4.2 Risk minimization

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

- Candidates with known sensitivity to insect repellents or skin care products are excluded. (p. 20)
- Subjects "will be monitored throughout the study and prompt medical attention will be obtained if any adverse reaction is observed." (p. 27)
- Candidates "known to be unduly sensitive to stable fly bites" are excluded from the repellent phase. (p. 20)
- "Subjects will only need to receive two bites within 30 minutes to confirm breakdown, after which the test arm will not be exposed to flies again." (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 flies.
- Only one untreated control to confirm stable fly aggressiveness; no positive controls.
- Exposure of untreated control for no more than 1 min/half hour in each cage; exposed arm will be withdrawn from each cage immediately following the second landing. (p. 32)
- 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?

"A 100-fold margin of exposure (MOE) is considered to be the target for the determination of acceptable risk from systemic exposure. The MOE is based on the No Observed Adverse Effect Level (NOAEL) for systemic effects, the concentration of active ingredient in the formulation, frequency and rate of application, skin surface area and body weight, and dermal absorption. The MOE for the test subjects in this efficacy study will substantially exceed the minimum 100-fold target and is, therefore, considered acceptable under widely recognized scientific standards." (p. 27)

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 20%; thus 835 mg of the repellent product is equivalent to 167 mg picaridin. Because the ethanol in both formulations increases percutaneous absorption, this figure is adjusted by an "ethanol enhancement" factor of 2.26, yielding an adjusted dose of 377 mg, roughly equivalent to 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, even in ethanol, 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.

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

"The test subjects will continue to expose their treated arms to stable flies until the FCB (First Confirmed Bite) or until 10 hours have elapsed, whichever occurs first. . . . When the two bites have occurred as noted above, the test will terminate on that arm." (p. 33)

(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." (pp. 27-28)

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

Test subjects "will be monitored throughout the study and prompt medical attention will be obtained if any adverse reaction is observed." (p. 27)

(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. 28)

"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 Principal Investigator any time after the study if you experience

[2] This calculation assumes a standard dose rate of 1 g/600 cm^2, or 1.67 mg/cm^2. The actual dose rate determined in the dosimetry phase of the proposed test may be higher or lower. Treated area is 250 cm^2 on each forearm. Dose of product on each arm is thus likely to be approximately 1.67 x 250 = 417.5 mg.

any study-related adverse effects, either before or after this follow up call." (pp. 89, 100)

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

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 for payment. ICR will incur the cost of any such study-related bills." (p.28)

"We will pay all of your medical bills for study-related illnesses and injuries." (pp. 89, 100)

5. Benefits

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

"You will get no personal benefit from participating in this study." (pp. 90, 100)

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

"Indirect benefit may accrue to society . . . by the development of more effective, safer and 'pleasant-to-use' repellent products, and alternatives to DEET-based products." (p. 28)

"The main benefit of this dose determination study is that it establishes the dose of the repellents to be tested in the subsequent stable fly repellent study. Some benefit may result for society . . . through showing the effectiveness of these products in repelling a noxious pest." (p. 90)

Some benefit may result for society . . . through showing the effectiveness of these products in repelling a noxious pest." (p. 100)

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

"The sponsor will gain the most benefit from this study through knowledge gained on the performance of its repellent products." (p. 28)

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

The testing is likely to demonstrate that the 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. Some societal benefit would be likely to result from identification of additional repellents effective against stable flies.

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 balance of risks to subjects and likely benefits to the sponsors and to society is not discussed in the protocol.

The protocol appropriately minimizes the risks to subjects. 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 directly address the likely benefit of the knowledge likely to be gained from the research, but rather presumes that knowledge would lead to market results of benefit to the sponsor and others.

Notwithstanding these limitations of the arguments concerning the expected benefit of this research, there is potential societal benefit in identifying registered products which effectively repel stable flies, and this identification can be performed reliably in the laboratory using disease-free flies. All in all, the residual risks to subjects are likely to be reasonable in light of the potential benefit to consumers of a wider range of choice in effective repellents of stable flies.

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) as of 29 Feb 2008. 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 supporting materials to the EIRB, the EIRB's conditional approval letter, minutes of the EIRB discussion, and the final EIRB approval letter 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 complies with the EPA's Final Rule governing the use of human test subjects, and adheres to 40 C.F.R. Part 26 Subparts K and L when it uses human subjects in studies." (p. 13)

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?

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?

"All candidates will review and sign an Informed Consent Document ("ICD") prior to acceptance as study subjects. The ICD will be formally explained to all candidates before the study is scheduled to begin. A candidate may visit ICR to review and sign the ICD or the ICD can be mailed to the candidate for their review. If mailed, the study director will phone the candidate to answer any questions regarding the ICD. If any candidate refuses to sign after learning the details of the document, they will not be allowed to participate in the study. After the ICD is fully described to the candidate, he or she may then sign the ICD in the presence of an ICR staff and a copy of the ICD will be made and returned to the candidate. He or she will then be notified within one week if they have been enrolled as a subject in the study." (p. 22)

(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 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." (p. 33)

"We will keep your participation as confidential as possible referring to you in the study data and reports only by your initials or an arbitrary ICR identification. However, . . . the sponsor, personnel associated with the study, a regulatory agency such as the Environmental Protection Agency (EPA), and the Essex Institutional Review Board (EIRB) all have a right to review your records." (pp. 92, 102)

"After signing the ICD and shortly before any treatment with a test articles, each female candidate will take a pregnancy test as described by the label of an over-the-counter pregnancy test kit supplied by ICR. This will apply to the dose determination phase (section 11 below) and to the repellent test phase (section 20 below). Any subject who shows a positive result will be discretely excluded from further participation. The presence of multiple female subjects will allow the reason for their exclusion to be kept private. A female ICR staff member will confirm the pregnancy test results. The study director will be advised of the results, but no one else will be. The reason for the positive subject's exclusion from the study will be kept private by the study director informing the other subjects that this subject has not been able to meet one of the inclusion or exclusion criteria, without specifying which one." (p. 23)

(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 Forms.

(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. (pp. 89, 100).

§ 26.1111 Criteria for IRB approval of research
ICR Protocol No: G4330108001A382 (Version of 2/1/2008)

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	Risks to subjects are very low, and notwithstanding poor characterization of societal benefits, offset by potential societal benefit of identifying registered repellents effective against stable flies
(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: G4330108001A382 (Version of 2/1/2008)

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. 84, 93
	(2) A description of any reasonably foreseeable risks or discomforts to the subject	OK	pp. 89; 98-100
	(3) A description of any benefits to the subject or to others which may reasonably be expected from the research	OK	p. 90, 100
	(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject	OK	p. 90, 101
	(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained	OK	p. 92, 102
	(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, 100. 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. 91, 101-102
	(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, 101
(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. 91, 101
	(3) Any additional costs to the subject that may result from participation in the research	OK	p. 90, 100
	(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	OK	p. 90, 101
	(6) The approximate number of subjects involved in the study	OK	p. 86, 95
(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. 84, 93

§26.1117 Documentation of informed consent
ICR Protocol No: G4330108001A382 (Version of 2/1/2008)

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	Dosimetry form pp. 84-92 Repellency form pp. 93-103
(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	

Attachment 5

40 CFR 26.1125 Prior submission of proposed human research for EPA review
ICR Protocol No: G4330108001A382 (Version of 2/1/2008)

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	pp. 110-210; 246-343 pp. 41-60
	(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	pp. 235-244 Conditional approval Unanimous Not addressed No controverted issues
	(3) Records of continuing review activities.		n/a	
	(4) Copies of all correspondence between the IRB and the investigators.		Y	pp. 7, 110, 211-225, 227-234, 246
	(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.		N Y	p. 243 names only. Degree shown only for Chairman. No info re experience or expected contributions p. 244 no conflicts of interest asserted
	(6) Written procedures for the IRB in the same detail as described in §26.1108(a) and §26.1108(b).		N	Separately submitted directly to EPA
	(7) Statements of significant new findings provided to subjects, as required by §26.1116(b)(5).		n/a	
The following Information, to the extent not already included:	§1125(a) a discussion of:	(1) The potential risks to human subjects	Y	pp. 26-28
		(2) The measures proposed to minimize risks to the human subjects;	Y	pp. 27-28
		(3) The nature and magnitude of all expected benefits of such research, and to whom they would accrue	Y	p. 28
		(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	
	§1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB.		Y	Original pp. 144-168; 173-191 Revised pp. 289-302; 323-342 Approved pp. 84-103
	§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.		Y	pp. 20-23; 104-106
	§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. 22-23
	§1125(e): All correspondence between the IRB and the investigators or sponsors.		Y	pp. 7, 110, 211-225, 227-234, 246
	§1125(f): Official notification to the sponsor or investigator . . . that research involving human subjects has been reviewed and approved by an IRB.		Y	p. 7