UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM:

September 21, 2009

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

FROM: Kelly Sherman
Human Research Ethics Reviewer

Kevin Sweeney
Science Reviewer

TO: Marion Johnson, Chief
Insecticide Branch, RD

REF: Carroll, S. (2009) Efficacy Test of KBR3023 (Picaridin; Icaridin)-Based Personal Insect Repellents (20% Cream and 20% Spray) with Ticks under Laboratory Conditions. Efficacy Test Protocol LNX-003. Unpublished document prepared by Carroll-Loye Biological Research. 152 p. (MRID 47836801)

Independent Investigational Review Board, Inc. (2009) Supplemental IIRB, Inc. Documentation Package. Unpublished compilation including IIRB, Inc. Human Research Protection Program Plan, IIRB, Inc. Membership Roster, and IIRB, Inc. Statement of Compliance. 111 p.

Supplemental Submission: Memorandum (dated 9/16/09) from Scott Carroll (CLBR) to Kelly Sherman and Kevin Sweeney (EPA) Providing Proposed Amended Language for Protocol LNX-003.

We have reviewed from both scientific and ethics perspectives the referenced protocol and supporting materials proposing a laboratory test of tick repellency. This review assesses the scientific aspects of the proposed research in terms of the recommendations of the draft EPA

Guidelines 810.3700 and of the EPA Human Studies Review Board, and the ethical aspects of the proposed research in terms of the standards defined by 40 CFR 26 subparts K and L and the recommendations of the EPA Human Studies Review Board.

A. Completeness of Protocol Submission

The submitted protocol was reviewed for completeness against the required elements listed in 40 CFR §26.1125. EPA's checklist is appended to this review as Attachment 5. All required elements are present.

In addition to the protocol itself (pp. 3-27) and the associated consent documents as approved by the Independent Investigational Review Board, Inc. (IIRB) (pp. 30-38), the following supporting documents were considered in this review:

- IIRB Approval letter of 7/30/09 (pp. 28-29)
- Data recording forms (pp. 39-50)
- Subject training materials for tick handling (p. 51)
- Labels and MSDSs for test products (pp. 52-63)
- Toxicology profile of KBR 3023 (pp. 64-65)
- HSR Training records for investigators (pp. 66-67)
- Index of CLBR-IIRB Correspondence (pp. 70-71)
- Protocol (dated 7/27/09) and supporting materials as originally submitted to IIRB (pp. 74-120)
- Email correspondence between Carroll-Loye Biological Research and Independent Investigational Review Board (pp. 121-122)
- IIRB Email Request for a Site Questionnaire for a single study site (p. 123)
- CLBR response, including completed Site Questionnaire for a single study site (pp. 123-133)
- IIRB Email with redline version of Informed Consent Form showing IIRB's requested changes (pp. 134-143)
- Minutes of 7/28/09 IIRB meeting (pp. 147-148)
- Email and Administrative Letter (dated 8/3/09) from CLBR to IIRB clarifying the correction of the discrepancy noted in IIRB's approval letter (pp. 144-145)
- IIRB Letter dated 8/4/09 acknowledging and approving CLBR's 8/3/09 administrative letter (p. 151)

Three required elements were submitted separately, and are combined in the "Supplemental IIRB, Inc. Documentation Package" cited above:

- IIRB, Inc. Human Research Protection Program Plan (5/12/09)
- IIRB, Inc. Membership Roster (1/6/09)
- IIRB, Inc. Compliance Statement (7/14/08)

B. Summary Assessment of Ethical Aspects of the Proposed Research

Here is a summary of our observations about the ethical aspects of the proposed protocol. Supporting details are in the attachment.

1. **Societal Value of Proposed Research:** This study will test the efficacy against ticks of two conditionally registered formulations containing the active ingredient Picaridin (KBR 3023) at 20% concentration. EPA requires efficacy testing of these specific formulations to support continued registration of the products. Direct testing of the duration of efficacy is important because consumers, who rely on repellents to avoid insect bites, cannot readily assess the efficacy of a product independent of EPA's approval. There is potential benefit to society in demonstrating effectiveness of picaridin tick repellents at this concentration, which users may prefer to other repellent products because of their cosmetic or other qualities.

2. **Subject Selection:** Subjects will be recruited from a "Volunteer Database" of previous subjects and others who asked to be added to the database. The database is racially diverse, 75% in the age range from 20-40 and 25% in the range 40-55. The youth and high education levels of candidates in the database reflect the university community where the laboratory is located. Explicit factors exclude as subjects children, pregnant or lactating women, those in poor health or physical condition, and those unable to speak and read English. The sample will thus not be fully representative of the population of potential repellent users. There is no indication that any subjects will be from populations vulnerable to coercion or undue influence.

3. **Risks to Subjects:** The protocol and consent form discuss risks of five kinds: risks from exposure to the test materials; risks of exposure to biting arthropods; risks from exposure to disease vectors; risks of physical stress in the test environment; and risks of stress from learning the results of a pregnancy test. All practical steps to minimize subject risks have been taken.

   The test material is accurately characterized in the Informed Consent Form as an eye irritant, harmful if swallowed—consistent with the required hazard statements on the registered product label.

   Because of the generally low acute and chronic hazard profile of the test material, the design of the research to minimize exposure, and the training of subjects to remove ticks before they bury and bite, the probability of the identified risks is accurately characterized as "extremely small."

4. **Benefits:** There are no direct benefits to subjects. This is made clear in the protocol and informed consent form. If the testing shows good efficacy, the direct beneficiary of the research is likely to be the sponsor. Indirect beneficiaries may also include repellent users who prefer these products to other repellents.

5. **Risk/Benefit Balance:** No practical opportunities to further reduce risk to subjects while maintaining the robustness of the scientific design have been overlooked. The residual risk to subjects is very low, and reasonable in light of the anticipated benefits of the research.

6. **Independent Ethics Review:** The Independent Investigational Review Board, Inc. (IIRB), of Plantation, Florida, has reviewed and approved the protocol and informed consent materials. IIRB is independent of the investigators and sponsors. Satisfactory documentation of IIRB procedures and membership was provided in the "Supplemental Documentation Package."

   The discrepancy noted in IIRB's approval letter of 7/30/09 (p. 28) regarding when subjects would be trained to handle ticks was clarified through an administrative letter from CLBR to IIRB dated 8/3/09 (p. 145), and acknowledged and approved by IIRB in a letter to CLBR dated 8/04/09 (p. 151).[1]

7. **Informed Consent:** The protocol contains a complete and satisfactory description of the process by which potential subjects will be recruited and informed and for seeking their consent to participate. A copy of the IRB-approved consent form meeting all requirements of 40 CFR §§26.1116 and 26.1117 is included in the protocol.

8. **Respect for Subjects**: Methods proposed for managing information about prospective and enrolled subjects are adequate to protect their privacy from compromise. Subject names and other personal information are linked on only one form to their arbitrary "subject number"; in all other data collection forms subjects are identified only by their assigned number.

   Subjects will be free to withdraw at any time, and will be reminded of this at several points before and during the research. Subjects who withdraw will be compensated for time spent up to the point of withdrawal. Medical care for research-related injuries will be provided at no cost to the subjects.

C. Compliance with Applicable Ethical Standards

This is a protocol for third-party research involving intentional exposure of human subjects to a pesticide, with the intention of submitting the resulting data to EPA under the pesticide laws. Thus the primary ethical standards applicable to this proposal are 40 CFR 26, Subparts K and L. In addition, the requirements of FIFRA §12(a)(2)(P) for fully informed, fully voluntary consent of subjects apply. Because the test will be conducted in California, the provisions of the California Code of Regulations, Title 3, §6710 apply as well, including provision to subjects of the "Experimental Subject's Bill of Rights" appearing on p. 38.

[1] The version of the protocol that appears on pp. 1-27is identical to the version approved by IIRB, except that the clerical error/discrepancy on line 762 has been corrected to note that training will occur within 30 days preceding test day.

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

The following specific deficiencies in the protocol should be addressed before the research is initiated:

- In the statement about compensation for research-related injuries (p. 6 of 8 of the consent form) please make the following clarifying revision:
    - Current Language: "Carroll-Loye Biological Research will cover the costs of such medical treatment that are not covered by your own insurance or by a third party that covers you."
    - Change to: "Carroll-Loye Biological Research will cover the costs of such medical treatment that are not covered by your own insurance or by the insurance of a third party under which you are covered."
- Lines 447-455: Items #14 and #15 are not properly included as "exclusion criteria" because they cannot be applied before subject enrollment: they are possible reasons for withdrawal of an enrolled subject. Please remove items #14 and #15 from the list of exclusion criteria, and revise the Stop Rules or other aspects of the protocol to incorporate this information.

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.

This 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 under laboratory conditions as a tick repellent of two registered repellent spray products containing picaridin. The main objective of the study is to quantify the efficacy of the formulations to repel actively questing ticks.

Active questing behavior of each tick will be verified by placing each tick on the untreated forearm of the subject. Ticks which do not move ("quest") in the direction of the elbow at least 3 cm within 3 minutes will not be used in the efficacy trial. Qualifying ticks will be placed one at a time on the wrist of the subject's treated arm, and monitored for 3 minutes to

determine whether they cross into the treated area of the arm or are repelled by the test material. The cycle of qualifying a tick on the untreated arm and then testing qualified ticks for repellency on the treated arm is repeated every 15 minutes from the time of application of the test material until efficacy failure, defined as a crossing into the treated area followed by another crossing within either of the two subsequent test periods. This cycle is repeated within each 15-minute period with the second tick species.

1. **Study design:** The protocol objective is to determine the efficacy of the two picaridin formulations, when applied at a typical consumer dose, in repelling the nymphal life stage of the American Dog tick, *Dermancentor variabilis*, and the black-legged tick, *Ixodes scapularis*. The efficacy study will be conducted in the laboratory. In each trial, each Test Material will be tested with 10 subjects. All subjects will be assigned to the treated group, which will be blocked by gender. Within each gender, the treatments will be allocated at random excepting minor adjustments needed to constrain the numbers treated with a particular test material to 10. The proposed distribution of treatments among subjects is summarized in the table on p. 20 of the protocol.

   The objective can be met by the study if the deficiencies described below are satisfactorily addressed—especially if an adequate description of testing the second tick species is added.

2. **Statistical design:** The general hypothesis of the research is that the test materials will substantially reduce the probability that a tick crosses a repellent treatment for several hours. However, more than testing that hypothesis, the aim of the research is to characterize the duration of repellency based on the Complete Protection Time criterion. Each subject is a replicate, and ten individual subject values for CPT will be obtained for each test material and averaged. The protocol states that it is possible that the study design could be fulfilled with only ten subjects, but it is unlikely that the same subjects will be used to test both formulations. In addition, 3 alternate subjects will be enrolled. No analysis of repeated measures is contemplated. A sample size of 10 per test material reflects a compromise between cost and precision; ten subjects are two-thirds more than the historical EPA requirement of six subjects; if relatively few values are censored, and particularly if the range of values is not great, a sample size of 10 should give excellent estimates of mean, median, and variation around those values, relative to historical standards.

   Each subject is treated on one forearm only; the untreated forearm serves as a control to confirm active questing behavior of each tick. Because the lotion and spray test materials are obviously different, efficacy testing will not be blinded. No positive control or negative vehicle control is proposed nor will the study compare the efficacy of these products to any other material. No direct comparisons of treated and untreated subjects (or arms) are contemplated in the statistical analysis plan. Repellency will be reported as "Complete Protection Time", calculated for each test material and each tick species as the mean time across all treated subjects from application of the repellent to the First Confirmed Crossing. The protocol is unclear about the reporting of CPT values. Data sheets are presented for collecting data with each tick species but as proposed they may

be analyzed separately for each tick species or may be combined and analyzed. Time of each crossing will be reported with a precision of 15-minute intervals; the average time across all subjects from treatment until First Confirmed Crossing by each tick species will be calculated, and standard deviation and 95% confidence interval will be reported. To examine the temporal pattern of repellent failure, the Kaplan-Meier survival analysis by subject will be employed. The Kaplan-Meier survival analysis accommodates some data censoring in the event that subject(s) withdraw or are withdrawn before failure. In addition, the Kaplan-Meier median will be estimated, and the time until 25% failure, for each test product reported. In the presence of a high frequency of censoring, median (and mean) values will be underestimated.

3. **How and to what will human subjects be exposed?** A standardized typical dose, expressed as volume per unit area, will be scaled to the measured surface area of each subject's forearm and applied by a technician. The standard application rate for the lotion (cream) is 2.51 $\mu l/cm^2$ while the spray is applied at the rate of 0.97 $\mu l/cm^2$. (It is possible for the dosing to change based on dosimetry data collected from the LNX-002 study. If this occurs, the protocol will be amended.) The repellent will remain in place for 12 to 14 hours during the test. In addition, subjects will be exposed to potential bites by lab-reared pathogen-free ticks (with very low probability), and (with extremely low probability) to arthropod-borne diseases.

4. **Endpoints and Measures:** A standard unit "typical consumer dose" will be used for each subject in the repellency phase. In the repellency phase, complete protection time (CPT) will be measured as the mean time from initial application of a typical consumer dose to the First Confirmed Crossing (FCC), and will be presented with standard deviation and 95% confidence interval. It is unclear in the proposed protocol whether or not CPT values will be reported separately for each ticks species or if they will be combined in some fashion. Subjects will be trained in the laboratory to handle ticks and observe their behavior, and to remove ticks before they have time to bury or bite. All crossings will be recorded by a research technician and included in the report of the research.

E. Compliance with Applicable Scientific Standards

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

- Quantification of efficacy of the test materials
- Data collection, compilation and summary of test results
- Justification for sample size in repellency phases

This protocol does not adequately address the following element:

- Experimental design appropriate for achieving scientific objectives

In order to ensure that the experimental design is adequate to achieve the scientific objectives, the following elements in the protocol require revision before the research goes forward:

- Lines 146-147: Please revise as follows: "The endpoint will be the time of failure expressed as the time of the FCC for each subject." Please add a statement indicating that an FCC will be recorded for each subject for each of the two tick species.

- Lines 211-213: Please clarify what it means for the repellent to "begin failing." If the language stating "removing any treated limb from the study when the repellent begins failing" is intended to mean that a subject will be removed from the study once a FCC has been noted, please revised the phrase accordingly.

- Lines 214-215: What is the basis for the estimate that exposures of treated and untreated skin will be for a maximum of 24 minutes per hour? Based on the reference in lines 732-733 to "3-minute exposure periods commencing once every 15 minutes" this appears simply to be the sum of 4 x 3 minutes for the untreated arm and 4 x 3 minutes for the treated arm during each hour. That would not allow for the possibility that more than one tick might have to be exposed to untreated skin to find one that was foraging avidly, nor for avidity screening and efficacy testing with both species in each 15-minute interval.

- Lines 607-609: "The 'negative control' for efficacy data sets serves to insure that each tick employed in the study is attracted to the test subject before it is used in a repellency challenge." Is this the "confirmation of subject attractiveness" mentioned in lines 565-566?

- Lines 697-703: This paragraph includes erroneous references to "three treatments."

- Lines 725-728: This section includes a cross-reference to §4.8.2.1, which does not exist.

- Line 734: Is it not the case that exposures would end only when the subject receives confirmation of a crossing by the second tick species? That would be consistent with the stop rule (line 756) calling for a confirmed crossing by both tick species. Note also that a subject cannot directly "receive" a FCC, since only later will the first crossing be confirmed by another.

- Lines 750-751: A stop rule applicable to "all subjects" is defined here as "foraging pressure falls below threshold needed to challenge the Test Materials." What does this mean? Foraging pressure is binary for each tick/subject pair—it must be either 1 or 0. What is the cited threshold needed to challenge the test materials

- Line 755: Another stop rule applicable to individual subjects is defined here as "subject proves unattractive to target species." How is this measured? Since this is treated as a stop rule rather than an exclusion factor, how much unattractiveness is permissible? Would unattractiveness to one species disqualify a subject, or would it have to be to both species?

- Lines 780-812 (section 4.8.3.1): Since the objective is to test repellency against two species of ticks (as is stated in lines 122-126, described in the CF, and indicated by separate data collection forms for each species on pp. 43-48), this description of the actual repellency testing procedure must account for testing of both species. As it stands it calls for testing only one tick in every 15-minute interval.

- Lines 837-846: This discussion of the statistical objectives needs to clarify that a separate result will be computed for each test species.

- Line 855: CPT will be measured as a single time value for each subject *for each tick species? or will the data be combined and reported?*

- Line 382: Please change 'principals' to 'principles'

A September 16, 2009, memorandum from Scott Carroll (CLBR) to Kelly Sherman and Kevin Sweeney (EPA, Office of Pesticide Programs) details CLBR's proposed revisions to the protocol to address many of the deficiencies identified in this review. If CLBR's proposed protocol revisions are implemented, and if any additional relevant deficiencies identified in this review or by the HSRB are corrected, the protocol is likely to achieve the scientific objectives.

Attachments:

1. Summary Review of Carroll-Loye Protocol LNX-003 dated 7/27/2009
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: LNX-003

Title: Efficacy Test of KBR3023 (Picaridin; Icaridin)-Based Personal Insect Repellents (20% Cream and 20% Spray) with Ticks under Laboratory Conditions.

Date: July 27, 2009

Principal Investigator and any sub-investigators:
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Participating Laboratories:
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1. Societal Value of Proposed Research

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

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

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

"Efficacy and duration will be measured as Complete Protection Time, or CPT, defined herein as the time between application of test material and the First confirmed Crossing of an actively foraging tick from the untreated skin surface of a subject's hand 3 cm or more into the treated forearm skin area. A 'First Confirmed Crossing' (FCC) is that which is followed by another within 30 minutes." (p. 5)

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

"The US Centers for Disease Control (CDC) has acknowledged the existence of substantial consumer interest in new and effective insect repellent products, including the choice of a variety of formulations, delivery systems, and concentrations of active ingredient. Of the three DEET-alternatives currently considered by CDC to have public health value, Picaridin probably has the highest broad-spectrum efficacy. However, few Picaridin products are currently available to US consumers. US EPA has requested new, US-based efficacy data as a condition of registration for the test products. The purpose of this study is to provide those efficacy data. The information will also be used in product labeling." (p. 6)

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

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

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

The concentration of KBR 3023 in this product is higher than that in other registered repellents containing it, so EPA requires product-specific efficacy data to support its registration. No previous testing of these products against ticks has been conducted.

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

"Human subjects are required because they represent the target system for the test material, and sufficiently reliable models for repellency testing have not been developed." (p. 6)

2. Study Design

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

"The objective of this study is to test the repellent efficacy characteristics of the test materials to ticks. . . . The general hypothesis of the research is that the test materials will substantially reduce the probability that a tick crosses a repellent treatment for several hours. However, more than testing that hypothesis, the aim of the research is to characterize the duration of repellency based on the Complete Protection Time criterion. Complete Protection Time . . . is defined herein as the time between application of test material and the First Confirmed Crossing.'" (p. 5)

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

The objective cited may be achieved by the study as proposed if the protocol is amended to address the testing with two tick species and how these data will be reported and analyzed.

2.1 Statistical Design

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

"In efficacy testing, we will engage 10 subjects per treatment. Each subject is a replicate. It is possible that a single set of 10 individuals could complete all parts of the study. It is much more likely that substantially more than 10 individuals will participate. …We will enroll three more subjects than are required to meet our sample size." (p. 16)

The rationale for this sample size appears on pp. 16-18. A sample size of 10 reflects a compromise between cost and precision; ten subjects are two-thirds more than the historical EPA requirement of six subjects; if a minority of values is censored, and particularly if the range of values is not great, a sample size of 10 should give an excellent estimates of mean, median, and variation around those values, relative to historical standards. (p. 17)

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

"Each subject simultaneously serves as a treatment and control subject. The 'negative control' for efficacy data sets serves to insure that each tick employed in the study is attracted to the test subject before it is used in a repellency challenge. Ticks that fail to meet the questing criterion (§4.8.2.1) are not used against Test Materials. In this way the negative control serves as a pre-screening of the ticks, such that only actively questing ticks are then exposed to the treatments. Based on this manipulation of a standard control design, the crossing rate on the negative control is judged to be 100%." (p. 18) This use of untreated controls to confirm active questing behavior of all ticks used in efficacy testing is appropriate for the study design.

"There are no controls by which each formulation matrix without the repellent active [ingredient] is tested. . . . Questions of comparison between the test materials and other repellents are external to the objective." (p. 18) There are no comparison materials or positive controls. Omission of matrix and comparison materials is appropriate for the study design. No direct comparisons of treated and untreated subjects (or arms) are contemplated in the statistical analysis plan.

(c) How is the study blinded?

The study is not blinded. (p. 21)

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

"Each subject simultaneously serves as a treatment and control subject." (p. 18)

"The efficacy study will consist of one laboratory trial. In each trial, each Test Material will be tested with 10 subjects. (p19) All subjects will be assigned to the treated group, which will be blocked by gender…Within each gender, the treatments will be allocated at random excepting minor adjustments needed to constrain the numbers treated with a particular test material to 10." (p. 20). A table on p. 20 summarizes the proposed distribution of treatments among subjects.

(e) Can the data be statistically analyzed?

Yes.

The application rate for each product will be a standard typical consumer dose derived from past dosimetry data developed by this laboratory for the same test materials. In the efficacy phase ten individual subject values for CPT will be obtained for each test material and tick species and averaged. No analysis of repeated measures is contemplated in the case that a single subject participates in more than one phase of the research.

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

"Statistics will be computed with SAS's JMP software, Version 5.0.1.2 (SAS Institute, Cary, NC)." (p. 24)

"Because all subjects use different ticks, all ticks are used only once, and neither organism interacts directly with conspecifics at the level of the skin and the repellent during data collection, we will analyze data by subject as independent, replicated values. . . . The objective is to compute, for each test material, a reasonable estimate of mean and standard deviation for the duration between application and sufficient repellency breakdown such that there are two ticks crossing on a subject within a half-hour period. In the efficacy phase "Complete Protection Time" (CPT) is measured as the length of time from initial application to the First Confirmed Crossing. A FCC is a Crossing followed by another Crossing within 30 minutes…CPT is measured as a single time value for each subject. . . . We will calculate mean CPT will be calculated across all 10 subjects, and will be presented with standard deviation and 95% confidence interval information. Data will be normalized as possible to enhance the value of confidence interval calculations." (p. 24)

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

- Exposure delay (min)-time between application and first exposure
- Minutes to First Confirmed Crossing (FCC) or end
- Complete Protection Time (CPT) –time between application and FCC" (p. 24)

There is no discussion on how data collected from testing two tick species will be analyzed and reported.

"To examine the temporal pattern of failure further, we will employ Kaplan-Meier survival analysis by subject. Kaplan-Meier survival analysis accommodates some data censoring in the event that any subjects withdraw or are withdrawn before failure. In addition, we will estimate the Kaplan-Meier median, and the time until 25% failure, for each test product. In the presence of a high frequency of censoring, median (and mean) values will be underestimated." (p. 25)

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

The proposed statistical measures for duration of repellency appear to be appropriate, and robust enough to be appropriate for either normally or non-normally distributed data provided the study director explains how data collected with each tick species will be treated and analyzed.

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

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

2.2 How and to what will human subjects be exposed?

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

The two test materials are registered by EPA as EPA Registration Number 39967-50 (20% Cream) and EPA Registration Number 39967-53 (20% spray). Efficacy data to support label claims for these products were required by EPA as a condition of the products' continued registration; EPA has agreed to the testing strategy.

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

A "typical consumer dose of 2.51 $\mu l/cm^2$ and 0.97 $\mu l/cm^2$ for the cream and spray products, respectively will be applied based on the results of past dosimetry studies with both of the test materials. This standard unit dose will be used for all subjects in the efficacy phase. One forearm of each subject will be treated; exposure to the repellent will be continuous throughout the period of the efficacy test.

As proposed, subjects will be exposed for approximately six of every 15 minutes during the efficacy phase to disease-free laboratory-reared deer ticks (*Ixodes scapularis*) and American dog ticks (*Dermacentor variabilis*). (p. 23) However, this value only accounts for the testing of one species and does not fully describe how testing of the second species will be conducted. Further clarification is required.

(c) What duration of exposure is proposed?

The repellency phase will last for 12-14 hours; the period of actual exposure is uncertain and will vary by subject, depending on the individual value of CPT.

2.3 Endpoints and Measures

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

"Subject measurements" are listed in §.4.5. They include subject forearm surface area, which may be measured or based on historical subject data as explained. "This data will be kept on file for each subject. Subjects will be re-measured bi-annually or if, when asked, they indicate they may have gained or lost weight or muscle mass on their limbs since their measurements were last taken." Volume of test materials delivered to the skin is described in §4.6. (p. 19)

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

- Exposure delay (min)-time between application and first exposure
- Minutes to First Confirmed Crossing (FCC) or end
- Complete Protection Time (CPT)–time between application and FCC" (p. 24)

Data forms are presented for two tick species, but the protocol does not describe the testing regime with two species.

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

- Alternate subjects will be enrolled to ensure adequate sample size
- Subjects will be trained to handle ticks and to remove them before they can bite
- All crossings and repulsions are verified and recorded by a research technician

(c) What QA methods are proposed?

"A separate, professional Quality Assurance Unit (QAU) will inspect the study. The QAU will report to the Study Director. Protocol Review and Comments must take place before data collection commences. In-Life Inspection must include observing the measurement and recording of key variables by subjects and researchers. In addition, the Final Report will be audited for completeness and accuracy. A QAU Statement will address compliance and noncompliance or any omissions in auditing.

Findings from the In-Life Inspection and the Final Report, as well as the QAU Statement, will be transmitted to both the Study Director and to the Sponsor Monitor." (p. 25)

Reports of QAU findings should also be incorporated into the final report.

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

"Mean CPT will be calculated across all 10 subjects per treatment, and will be presented with standard deviation and 95% confidence interval." (p. 24) The protocol does not state if the CPT will be reported separately for each ticks species or if the CPT values for each species will be combined.

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 tick repellents. Little information is available to characterize this population, but it is presumed that repellent users are highly diverse in age, gender, physical size, general health, attractiveness to questing ticks, and other characteristics. The population from which subjects are recruited appears to be chosen largely on the basis of convenience, and is not screened for past or likely future use of repellents.

(b) From what populations will subjects be recruited?

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

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

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

"In general, about three-quarters of the subjects are age 20-40, with the remainder between 40 and 55. Final composition is not determined until enrollment is completed. The relevant demographics of the participants will be reported." (p. 11)

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

"Based on review of the scientific literature regarding individual differences in repellent performance and attractiveness to ticks, we conclude that this study's deviations from the ideal frame will not influence the representativeness of the results, or their generalizability to the greater population. Lastly, because our Volunteer Database cohort is comprised by individuals who regularly spend time in outdoor setting (and thereby may have relatively frequent encounters with biting arthropods), this group is probably appropriate for insect repellent users in general. " (pp. 12-13)

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

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

Yes.

3.2 Equitable Selection of Subjects

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

Inclusion:

1. Age 18-55;
2. Written consent; and
3. Speak and read English. (p. 13)

Exclusion:

1. Hypersensitivity to tick bites or exhibiting hypersensitivity during test;
2. Phobic of ticks;

3. Known to be allergic to repellents or common cosmetics;
4. Known to be sensitive to any of the test product ingredients;
5. Poor physical condition;
6. Unwilling to submit to brief query about personal condition;
7. Use of insect repellent within one day proceeding the efficacy test;
8. Unwilling to refrain from use of perfumed products, alcoholic beverages or smoking after 9 pm the evening preceding the efficacy test and throughout that test;
9. Known to be pregnant or lactating;
10. Unable to deliver the test materials or nymphal ticks to own left and right arms;
11. Unable to see nymphal ticks on skin or otherwise effectively monitor them on skin;
12. Student or employee of Study Director;
13. Does not regularly spend time in outdoor settings;
14. Withdraws from testing before receiving a confirmed crossing, when the total exposure duration is less than 90% of the mean exposure duration of subjects who did not withdraw, and when not more than 2 of 10 subjects have so withdrawn; and
15. Not attractive to target species. (pp. 13-14)

Items #14 and #15 are not "exclusion criteria" because they cannot be applied before subject enrollment. They are possible reasons for withdrawal of an enrolled subject.

The other criteria for inclusion and exclusion appear appropriate.

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

Subjects are recruited from "the community in which [the Investigator's] business is located . . . . Over time, we have developed a Volunteer Database of individuals who have expressed interest in participating in future repellency tests, provided contact information, and asked us to contact them. Initial recruiting is from this database, then from word-of-mouth of volunteers." (p. 11)

Students and employees of the Study Director are excluded from participation. (p. 14)

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

No subjects from a vulnerable population are proposed.

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

The recruiting/informing process to be used is described in the protocol on pp. 14-15.

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

Students and employees of the Study Director are excluded from participation. (p. 15) No eligible subjects are potentially subject to coercion or undue influence.

3.3 Remuneration of Subjects

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

"[E]ach research study participant will receive a cash payment of $20 per hour…If you are designated as an 'alternate subject' you will be paid for the hours you spent being trained, plus you will receive a payment of $50 to compensate for being inconvenienced." (p. 36)

(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 made at the end of each visit or whenever you withdraw from the study." (p. 36)

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?

"A complete toxicology package required for the registration of an insecticide including acute and subchronic neurotoxicity and metabolism studies was conducted. . . . KBR 3023 and its formulated products have low acute toxicity by oral, dermal, or inhalation routes of exposure. They were not irritating to the skin nor sensitizers in the animal studies. A slight to moderate ocular irritation was observed in the animal studies." (p. 64)

The cream formulation bears the signal word "Warning" because the product causes "substantial but temporary eye injury." (p. 52)

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

The protocol discusses risks of five kinds: risks from exposure to the test materials; risks from exposure to biting arthropods; risks from exposure to disease vectors; risks of physical stress in the test environment; and risks of stress from learning the results of a pregnancy test. Each class of risk and the steps taken to minimize it is discussed in pp. 6-9. The same classes of risk are characterized in the informed consent documents on pp. 34-35.

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

No numerical probability is estimated. Potential subjects are told (with respect to the risks of tick bites and of contracting an arthropod-borne disease or tick paralysis) "[t]icks require many minutes to bite through the skin, and we do not expect them to attempt to bite you during the study. The artist's paintbrush that we will train you to use to handle ticks will also be used to remove any ticks before they bite or bury in the skin. The ticks have been screened for infectious diseases at the US Centers for Disease Control and have been determined to be free of the pathogens that cause Lyme Disease, Rocky Mountain Spotted Fever, Ehrilichiosis, and Anaplasmosis." (p. 34)

4.2 Risk minimization

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

- The risk of a skin reaction to an insect bite is reduced by excluding candidate subjects who are aware of having a history of such reaction.
- Candidates with known allergic reactions to insect repellents and common cosmetics are excluded.
- Subjects will be trained to handle ticks and observe their behavior and to remove ticks from their arms before they have time to bury and bite.
- Ticks will be lab-reared and pathogen-free.
- First Aid materials will be available on-site.
- Epi-Pens will be on-site to treat anaphylactic allergic reactions.
- A physician who has read the protocol and discussed the research with the Study Director will be on call on the day of field testing.
- Results of pregnancy testing will be observed by one female technician only and never recorded to minimize the stress on a female subject testing positive, and minimize the possibility that other staff or subjects may become aware of the results of that test.

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

The actual dose rates are to be 2.51 µl/cm^2 and 0.97 µl/cm^2 for the cream and spray products, respectively. Based on treatment of an arm surface area of 600 cm^2 each treated subject will receive a dose of about 1506 µl (1506 mg) of the cream product or 582 µl (570 mg) of the spray product. The concentration of the test materials is 20% picaridin each, equivalent to 301 mg picaridin for the cream and 114 mg for the spray. Because of the ethanol in the spray formulations this figure is adjusted by an "ethanol enhancement" factor of 2.26, yielding an adjusted dose of 258 mg (3.7 mg/kg for a 70 kg adult) for the 20% spray. No ethanol enhancement factor is needed for the 20% cream, so application of 301 mg picaridin would be equivalent 4.3 mg/kg for a 70 kg adult.

The NOAEL for acute dermal toxicity in the rat for picaridin is 2000 mg/kg body-weight, 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/absorption. Thus, as a worst case based on exposure to the 20% cream application, the estimated margin of exposure (MOE) for picaridin acute dermal toxicity is 2000mg/kg/4.3mg/kg ,or MOE = 465.

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

"Stop Rules
All subjects
Consented duration reached
Test site becomes unsafe for subjects for any reason
Foraging pressure falls below threshold needed to challenge the test material(s)

Individual subjects
Subject asks to withdraw
Subject proves unattractive to target species
Subject's treated limb receives Confirming Crossings for both target species
Medical management is invoked for the subject (§1.3.6)" (p. 22)

CLBR should define what is meant by the stop rule "foraging pressure falls below threshold needed to challenge the Test Materials" and specify what threshold is needed to challenge the test materials.

CLBR should define what is meant by the stop rule "subject proves unattractive to target species" and clarify how it will be measured.

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

"If you are injured as a result of being in this study, a consulting physician who is aware of the study will be contacted immediately by telephone. Medical treatment will be available from a health care facility." (p. 35)

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

"Subjects are clearly and repeatedly informed that they may remove themselves for any reason from the study at any time, without penalty to their compensation. All subjects are asked to contact the Study Director and a physician of their own choice at any time should they develop a rash (a delayed hypersensitivity reaction) within 48 hours of the conclusion of the test day.

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

"When medical management is implemented, the Study Director will contact the On-Call physician for the study and comply with the physician's instructions. On the day of testing, a physician who has read the protocol and discussed the research with the Study Director will be on call. Contact information for the nearest medical facilities and maps from the test site to the facilities will be prepared and on file before the day of testing. In unlikely event of a Type 1 allergic reaction (anaphylaxis), we will contact 9-1-1 by cellular or satellite telephone and cooperate as instructed with emergency personnel. Epi-Pens will be on-site. At least one qualified researcher will remain with the other test subjects if other researchers depart with an injured or ill subject. We will be prepared to instruct emergency personnel on how to reach our site via multiple routes. In addition, we will personally transport affected persons to the nearest hospital if so advised by emergency personnel. There is sufficient redundancy in personnel that in such a case subjects remaining at the study site will still receive appropriate technical, scientific and safety guidance.

"Subjects may also request access to standard first aid materials (such as bandages, antiseptics, and mild topical and oral antihistamines) and request qualified first aid assistance at any time.

"As part of Medical Management, the Study Director will record all benign and adverse health observations." (pp. 8-9)

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

"Contact a physician and the Principal Investigator if you develop a rash within 7 days after the day of testing." (p. 34) Irritant or allergic reactions to the test materials or to tick bites are likely to occur shortly after exposure. Therefore, the seven-day period provides long enough duration to discover adverse events

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

"Carroll-Loye Biological Research will cover the costs of such medical treatment that are not covered by your own insurance or by a third party that covers you. If necessary, Carroll-Loye Biological Research will transport you to receive medical attention and pay costs associated with the reasonable and appropriate treatment for any injuries incurred as a result of participation in the study." (pp. 35)

The statement above about compensation for research-related injuries (p. 6 of 8 of the consent form) should be revised as follows:

- Current Language: "Carroll-Loye Biological Research will cover the costs of such medical treatment that are not covered by your own insurance or by a third party that covers you."
- Change to: "Carroll-Loye Biological Research will cover the costs of such medical treatment that are not covered by your own insurance or by the insurance of a third party under which you are covered."

5. Benefits

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

"There are no immediate benefits to you from your participation." (p. 35)

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

"The principal beneficiary will likely be the Sponsor, for whom new data and new labeling will meet current U.S. EPA registration standards…For the general public, tick-borne disease is of growing significance in the United States and around the world where U.S. citizens are active. Moreover, discomfort associated with nuisance biting restricts many work and pleasure activities." (p. 9)

"[B]y serving as a participant you may assist in making new insect repellent products available to consumers." (p. 35)

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

"The principal beneficiary will likely be the Sponsor, for whom new data and new labeling will meet current U.S. EPA registration standards." (p. 9) Indirect beneficiaries would include those repellent users who prefer these formulations to other available repellents.

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

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

6. Risk/Benefit Balance

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

The protocol systematically reduces risks to subjects without reducing the robustness of the scientific design. No reasonable opportunities to further reduce subject risk have been overlooked. The resulting residual risk to subjects is very low. The potential benefits to repellent users from availability of a wider variety of effective tick repellents are likely to be realized, and make the residual risks to subjects in this proposed research reasonable.

7. Independent Ethics Review

(a) What IRB reviewed the proposed research?

Independent Investigational Review Board, Plantation FL

(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?

Not reported. IIRB is not listed as accredited on the AAHRPP website.

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

Not reported. IIRB 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?

Complete records of the IRB review are provided in the protocol submission.

Satisfactory documentation of IIRB, Inc., policies and procedures and of IIRB, Inc., membership was submitted in addition to the protocol.

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

"U.S. EPA Good Laboratory Practice Regulations (40 CFR 160); 40 CFR 26 subparts K and L; FIFRA §12(a)(2)(P); California State EPA Department of Pesticide Regulation study monitoring (California Code of Regulations Title 3, Section 6710)." (p. 1)

8. Informed Consent

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

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

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

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

100%. English literacy is a requirement for participation.

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

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

Frequent opportunities to ask questions.

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

See protocol pp. 14-15 and consent form (pp. 30-37)

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

Candidates are offered repeated opportunities to decide not to participate; participants are offered repeated opportunities to withdraw. Exclusion factors rule out participation by employees or students of the Study Director. Recruitment of alternate subjects reduces the likelihood that subjects might 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?

"Carroll-Loye Biological Research will retain records of this study indefinitely. You may access your own records by contacting the Study Director. Representatives from the sponsor (LANXESS Corporation), the U.S. Environmental Protection Agency (EPA), the California Department of Pesticide Regulation and the Independent Investigational Review Board, Inc. (an independent committee that reviewed this study's ethical aspects to help protect the rights and welfare of study participants) may have access to all non-personal information collected in this study. Because of the need to release information to these parties, absolute confidentiality cannot be guaranteed. Any information or reports published as a result of this study will not identify you by name, or by any other personal identification." (p. 36)

"Results of a subject's [pregnancy] test are only observed by one female CLBR staff technician and never recorded to minimize stress on a female subject testing positive, and minimize the possibility that other staff or subjects may become aware of the results of that test." (p. 8)

Subjects are identified by name and subject number on the "Confidential Test Subject Information" form (p. 39). On all other data collection forms, only the subject number is used. 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 interview (pp. 14-15) and in the consent form.

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

Subjects who decide not to participate will simply go their way. Subjects identified as alternates, and any who withdraw from the research, will be paid for their time (p. 36).

§ 26.1111 Criteria for IRB approval of research
Protocol LNX-003 (7/27/09)

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

§26.1116 General requirements for informed consent
Protocol LNX-003 (7/27/09)

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		Y	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		Y	
The information that is given to the subject or the representative shall be in language understandable to the subject or the representative		Y	Information is clearly presented in plain 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		Y	The IC contains no exculpatory language
(a) In seeking informed consent the following information shall be provided to each subject	(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental	Y	p. 30
	(2) A description of any reasonably foreseeable risks or discomforts to the subject	Y	pp. 34-35
	(3) A description of any benefits to the subject or to others which may reasonably be expected from the research	Y	p. 35
	(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject	Y	p. 35
	(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained	Y	pp. 36
	(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	Y	Compensation p. 36 Medical Treatment pp. 35
	(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	Y	p. 35
	(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	Y	p. 36
(b) When appropriate, one or more of the following elements of information shall also be	(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	Y	p. 34
	(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent	Y	p. 36
	(3) Any additional costs to the subject that may result from participation in the research	Y	p. 36
	(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject	Y	p. 36
	(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	Y	p. 31
(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.		Y	p. 30

§26.1117 Documentation of informed consent
Protocol LNX-003 (7/27/09)

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.	Y	Consent form pp. 30-37
(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	Y	Consent form meets requirements of §26.1116; procedure described in protocol §3.4 provides adequate opportunity to read it before it is signed.
(b)(2) The consent form may be a short form written consent document stating that the elements of informed consent required by §26.1116 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative, in addition to a copy of the short form.	N/A	

40 CFR 26.1125 Submission of proposed human research for EPA review
Carroll-Loye LNX-003 (7/27/2009)

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

Requirement			Y/N	Comments/Page Refs
The following Information, to the Extent not already included:	§1125(a) a discussion of:	(1) The potential risks to human subjects	Y	pp. 6-8
		(2) The measures proposed to minimize risks to the human subjects;	Y	pp. 6-8
		(3) The nature and magnitude of all expected benefits of such research, and to whom they would accrue	Y	p. 9
		(4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and	Y	p. 6
		(5) The balance of risks and benefits of the proposed research.	Y	pp. 6-9
	§1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB.		Y	pp. 101-109 (submitted) pp. 30-38 (approved)
	§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.		Y	pp. 13. No advertisements used
	§1125(d): A description of the circumstances and methods proposed for presenting information to potential human subjects for the purpose of obtaining their informed consent.		Y	pp. 14-15
	§1125(e): All correspondence between the IRB and the investigators or sponsors.		Y	pp. 28-29, 70-152
	§1125(f): Official notification to the sponsor or investigator. . . that research involving human subjects has been reviewed and approved by an IRB.		Y	pp. 28-29
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. 3-27 None accompanied the proposal p. 30-38 Initial review of new proposal
	(2) Minutes of IRB meetings . . . in sufficient detail to show • attendance at the meetings; • actions taken by the IRB; • the vote on these actions including the number of members voting for, against, and abstaining; • the basis for requiring changes in or disapproving research; • a written summary of the discussion of controverted issues and their resolution.		 Y Y Y n/a n/a	 pp. 147-148 pp. 147-148 pp. 147-148 pp. 147-148 No controverted issues
	(3) Records of continuing review activities.		n/a	n/a for protocols
	(4) Copies of all correspondence between the IRB and the investigators.		Y	Provided by investigator pp. 70-152
	(5) • A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; • any employment or other relationship between each member and the institution, for example, full-time employee, a member of governing panel or board, stockholder, paid or unpaid consultant.		Y Y	Submitted separately
	(6) Written procedures for the IRB in the same detail as described in §26.1108(a) and §26.1108(b).		N	Submitted separately
	(7) Statements of significant new findings provided to subjects, as required by §26.1116(b)(5).		n/a	n/a for protocols