September 9, 2010

EPA-HSRB-10-01

Paul Anastas, PhD
EPA Science Advisor
Office of the Science Advisor
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Subject: June 23, 2010 EPA Human Studies Review Board Meeting Report

Dear Dr. Anastas,

The United States Environmental Protection Agency (EPA or Agency) requested that the Human Studies Review Board (HSRB) review two completed repellent efficacy studies conducted by Carroll-Loye Biological Research, Inc. (CLBR) of Davis, California. These two studies involved intentional exposure of human volunteers to picaridin-containing insect repellents. The Agency proposes to rely on these two studies, conducted after publication of the EPA's expanded final rule for protection of subjects in human research (40 CFR 26) on February 6, 2006 (71 Federal Register 24, 6137), for regulatory actions under the pesticide laws.

The Agency also provided the HSRB with updates on two additional topics: revised Agency guidelines for performance testing of topically applied repellent products, to be released for use by investigators and sponsors of new studies; and the recent settlement agreement reached between the Agency and six external parties to resolve litigation related to EPA's 2006 rule for the protection of human subjects of research.

The enclosed report provides the Board's response to EPA charge questions presented at the June 23, 2010 meeting. In addition, the report includes some additional recommendations for the Agency's repellent testing guidelines before release.

Assessment of Completed Carroll-Loye Biological Research Study LNX-002: Efficacy Test of KBR 3023 (Picaridin, Icaridin) - Based Personal Insect Repellents (20% Cream and 20% Spray) with Black Flies Under Field Conditions.

Science

- The Board concurred with the Agency's assessment that this study provides scientifically valid results to assess the repellent efficacy against black flies for the formulations tested.

Ethics

- The Board concurred with the Agency's assessment that the study submitted for review was conducted in substantial compliance with subparts K and L of 40 CFR 26.

Assessment of Completed Carroll-Loye Biological Research Study LNX-003: Efficacy Test of KBR 3023 (Picaridin; Icaridin) - Based Personal Insect Repellents (20% Cream and 20% Spray) with Ticks Under Laboratory Conditions.

Science

- The Board concurred with the Agency's assessment that this study provides scientifically valid results to assess the repellent efficacy against ticks for the formulations tested. However, the high frequency of participants for whom the repellent's protection time exceeded the long duration of the study creates statistical challenges in evaluating a specific protection time.

Ethics

- The Board concurred with the Agency's assessment that the study submitted for review was conducted in substantial compliance with subparts K and L of 40 CFR 26.

Revised Agency Guidelines for Performance Testing of Topically Applied Insect Repellents

The Board was not given a charge for consideration of the revised guidelines, but did have several comments designed to enhance the utility of the document. The Board felt that the revised Agency guidelines will provide sponsors and researchers with helpful guidance in the design of future efficacy tests of topically applied insect repellents. Before releasing these revised guidelines publicly, however, the Board recommended several changes or clarifications, including:

- Removal of the maximum-likelihood method requirement in the data analysis section;
- Clarification of recommendations regarding the use of positive controls, particularly with respect to the number of controls and the rationale for including them in the study;
- Careful consideration of recommendations regarding the recruitment and inclusion of so-called 'vulnerable' populations; and
- Encouraging the use of study designs that will enable investigators to collect data that will allow quantitative measurement of repellent efficacy in addition to determining the complete protection time (CPT).

Finally, as at previous meetings, the Board underscored that it would continue to evaluate protocols submitted for review to the HSRB based on appropriate statistical assumptions and analytic plans and thus might recommend rejection of a protocol even if it followed the revised Guidelines explicitly.

Sincerely,

Sean Philpott, PhD, MSBioethics
Chair
EPA Human Studies Review Board

NOTICE

This report has been written as part of the activities of the EPA Human Studies Review Board, a Federal advisory committee providing advice, information and recommendations on issues related to scientific and ethical aspects of human subjects research. This report has not been reviewed for approval by the Agency and, hence, the contents of this report do not necessarily represent the view and policies of the Environmental Protection Agency, nor of other agencies in the Executive Branch of the Federal government, nor does the mention of trade names or commercial products constitute a recommendation for use. You may obtain further information about the EPA Human Studies Review Board from its website at http://www.epa.gov/osa/hsrb. You may also contact the HSRB Designated Federal Officer, via e-mail at phre@epa.gov

In preparing this document, the Board carefully considered all information provided and presented by the Agency presenters, as well as information presented by public commenters. This document addresses the information provided and presented within the structure of the charge by the Agency.

US ENVIRONMENTAL PROTECTION AGENCY
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Jim Downing, Executive Director, Human Studies Review Board Staff, Office of the Science Advisor, United States Environmental Protection Agency, Washington, DC

*Not in attendance at June 23, 2010 Public Meeting

INTRODUCTION

On June 23, 2010, the United States Environmental Protection Agency's (EPA or Agency) Human Studies Review Board (HSRB) met to address scientific and ethical issues concerning: two completed repellent efficacy studies involving two registered insect repellents containing picaridin conducted subsequent to publication of the EPA's expanded final rule for protection of subjects in human research. In accordance with 40 CFR 26.1602, EPA sought HSRB review of these completed studies. Each of these completed studies is discussed more fully below.

In addition, the Agency provided the HSRB with updates on two additional topics: the revised Agency guidelines for performance testing of topically applied repellent products, to be released for use by investigators and sponsors of new studies; and a recent settlement agreement reached between the Agency and six external parties to resolve litigation related to EPA's 2006 rule for the protection of human subjects of research. A summary of the Board's conclusions concerning the Agency's revised guidelines for performance testing of topically applied repellent products is also provided below.

REVIEW PROCESS

On June 23, 2010, the Board conducted a public face-to-face meeting in Arlington, Virginia. Advance notice of the meeting was published in the Federal Register as "Human Studies Review Board; Notice of Public Meeting" (75 Federal Register 109, 32461).

Following welcoming remarks from Agency officials, the Board heard presentations from EPA on the following topics: two completed insect repellent efficacy studies involving intentional human exposure to two registered insect repellents containing picaridin (LNX-002 and LNX-003) conducted by Carroll-Loye Biological Research, Inc. (CLBR) of Davis, CA.

The Board also asked clarifying questions of several study sponsors and/or research investigators, including:

Dr. Scott Carroll, Principal, CLBR
Mr. Shawn King, Director of Operations, CLBR

Oral comments were provided by:

Dr. Scott Carroll, Principal, CLBR

No written public comments were provided.

For their deliberations, the Board considered the materials presented at the meeting, oral comments, and Agency background documents (e.g., published literature, sponsor and investigator research reports, study protocols, data evaluation records, and Agency science and

ethics reviews of proposed protocols and completed studies). A comprehensive list of background documents is available online at http://www.regulations.gov.

CHARGE TO THE BOARD AND BOARD RESPONSE

Assessment of Completed Carroll-Loye Biological Research Study LNX-002: Efficacy Test of KBR 3023 (Picaridin; Icaridin) - Based Personal Insect Repellents (20% Cream and 20% Spray) with Black Flies Under Field Conditions.

Overview of the Study

LNX-002 was a field-based study to measure the effectiveness of picaridin as a black fly repellent when used in one of two compound formulations (20% picaridin KBR 3032 All-Family Insect Repellent Cream and 20% picaridin KBR 3023 All-Family Insect Repellent Spray).

A total of 25 participants (selected from a pool of 119 volunteers diverse in age and ethnicity) participated in this study. There were 15 participants (8 female and 7 male) in the dosimetry phase. Twenty treated and two untreated volunteers participated in the efficacy test, with three more subjects serving as alternates. Ten participants tested each product formulation.

Dosimetry data accumulated in a previous CLBR study (LNX-001), along with additional dosimetry data collected from 15 volunteers in LNX-002, were used for dose selection. For the spray product each participant received 0.97µl/cm^2 of product, equivalent to 0.9312 mg product/µl. For the cream product, the volumetric dose rate was 1.94 µl/cm^2, equivalent to 1.9012 mg product/µl. For the spray product the mean picaridin dose was 98 mg per participant and 202 mg/participant for the cream product. The Margin of Exposure (MOE; how many fold lower the average human exposure is than the dose known to cause toxicity in animal models) calculations were based on an assumed 70 kg participant and the acute dermal LD50 value for picaridin at the limit dose of greater than 2,000 mg/kg. For the cream product the MOE = 690 and for the spray product the MOE = 1429, both values exceed the target MOE = 100.

The efficacy of picaridin as a black fly repellent was determined in a study conducted at a field site in the Mojave Desert of Southeastern California. Ten participants each were randomly assigned to one of two repellent treatments at the site for a total of ten volunteers per treatment. Each treatment was applied to an equal number of males and females. Participants were treated approximately 2.5 hours before field exposure. Untreated controls and participants treated with repellent were exposed to black flies for one minute every 15 minutes until the repellent failed. Treated participants were partnered in groups of two and each partner monitored the front of their own exposed forearm and the back of their partner's forearm. Black flies landing with intent to bite (LIBe) were recorded, aspirated into containers, and identified in the laboratory. Participants remained in the test until the repellent failed as determined by the first confirmed LIBe, or until the end of the test period, whichever came first. The time at which the repellent failed equaled the CPT for each subject.

Eleven of the 20 volunteers experienced a confirmed LIBe. Mean CPT values were not significantly different for the two formulations, with mean CPT calculated at 9.9 h for both products. Median CPT values also were calculable for both products and were nearly the same, 10.1 h for the cream product and 9.8 h for the spray product.

Science

Charge to the Board

Is the CLBR study LNX-002 sufficiently sound, from a scientific perspective, to be used to estimate the duration of complete protection against black flies provided by the test repellents?

Board Response to the Charge

HSRB Recommendation

The Board concurred with the Agency's assessment (Sweeney 2010a) that this study provides scientifically valid results to assess the repellent efficacy against black flies for the formulations tested.

HSRB Detailed Recommendations and Rationale

This study (Carroll 2010a; Carroll 2010c) was conducted according to a protocol that had been amended to take into account recommendations of the EPA and the HSRB (EPA HSRB 2009a).

The conduct of the dosimetry study and the field study were very similar to the conduct of previous field repellent efficacy studies conducted by CLBR.

The study was carefully conducted, with both sexes represented among the participants and the endpoint being the first LIBE) for each participant. The MOEs were high enough to not be a significant factor in the use of either formulation.

The protocol had one scientific deviation that was considered minor. Namely, a black fly species not named in the protocol was present during field testing. Board members felt that this deviation did not materially affect the scientific integrity and validity of the study.

Ethics

Charge to the Board

Does available information support a determination that study LNX-002 was conducted in substantial compliance with subparts K and L 40 CFR Part 26?

Board Response to the Charge

HSRB Recommendation

The Board concurred with the Agency's assessment (Carley 2010a) that the study submitted for review was conducted in substantial compliance with subparts K and L of 40 CFR 26.

HSRB Detailed Recommendation and Rationale

The documents provided by CLBR (Carroll 2010a; Carroll 2010c) state that the study was conducted in compliance with the requirements of the US EPA Good Laboratory Practice Regulations for Pesticide Programs (40 CFR 160); 40 CFR 26 subparts K, L and M; FIFRA § 12(a)(2)(P); and the California Code of Regulations Title 3, Section 6710. The study was reviewed and approved by a commercial human subjects review committee, Independent Institutional Review Board Inc. (IIRB, Inc.) of Plantation, FL. Documentation provided to the EPA indicated that IIRB, Inc. reviewed this study pursuant to the standards of the Common Rule (45 CFR Part 46, Subpart A) and found it in compliance. IIRB, Inc. also reviewed and approved Amendment 1 of October 30, 2009 (Carley 2010a; IIRB, Inc. 2010).

1. The Board concurred with the conclusions and factual observations relating to the study, as detailed in the EPA's Ethics Review (Carley 2010a). Specifically:

   a. *Prior HSRB and Agency Review.* The requirements of 40 CFR §26.1125 for prior submission of the protocol to EPA and of §26.1601 for HSRB review of the protocol were satisfied. The study (Carroll 2010a; Carroll 2010c) was conducted in accordance with the protocol previously approved by the HSRB (EPA HSRB 2009a). The Agency's ethics review of May 18, 2009 identified no deficiencies requiring correction relative to 40 CFR 26, subparts K and L, or to FIFRA § 12(a)(2)(P) (Carley 2010a). Because the study was conducted in California, the approval of CDPR was also required before the study could be initiated. CDPR granted final approval of the amended protocol and supporting documents on September 14, 2009.

   b. *Responsiveness to HSRB and Agency Reviews.* Following the HSRB review, the protocol and consent form were modified through Amendment 1 of August 13, 2009 (Carley 2010a; Carroll 2010c). This amendment incorporated changes responsive to the comments of EPA, the HSRB, and California Department of Pesticide Regulation (CDPR), as well as additional corrections initiated by the investigators and, at the request of the sponsor, provision for collecting additional dose-determination data for the cream formulation, to be pooled with that originally collected in study LNX-001. Agency suggestions were also addressed satisfactorily in Amendment 1. The reference to third party coverage of costs of medical treatment noted by the HSRB was revised in Amendment 1. IIRB, Inc. granted approval to Amendment 1 and supporting documents on August 18, 2009 (Carley 2010a; Carroll 2010c).

   c. *Substantial Compliance with Reporting Requirements (40 CFR §26 subpart M).* The primary study report initially failed to address the requirement of 40 CFR §26 subpart M, §26.1303(b) to submit copies of "official notification to the sponsor or investigator ... that

research involving human subjects has been reviewed and approved by an IRB." This omission was corrected by the submission of a supplemental document catalogued as MRID 48071301 (Carroll 2010c). Taking the two submissions together, along with the separately submitted documents reporting the roster and procedures of the IIRB, Inc., (2010), the requirements of 40 CFR §26.1303 to document the ethical conduct of the research were fully satisfied. Several Board members also remarked that, while current regulations only require "substantial" compliance with these reporting requirements, the submitted documents and supplementary materials from IIRB, Inc. met fully the regulatory reporting requirements. However, some Board members raised concerns about the regulatory meaning of the term "substantial" in the absence of clear parameters or guidance.

2. The Board concluded that this study met all applicable ethical requirements for research involving human participants, in accordance with the following criteria that had been stated in the Board's prior review of this study protocol:

   a. *Acceptable risk-benefit ratio.* The risks to study participants were minimized appropriately and were justified by the potential societal benefits, particularly data on the efficacy of these new formulations as personal insect repellents.

      - Minors and pregnant or lactating women were excluded from participation, with pregnancy confirmed by over-the-counter pregnancy testing on the day of study or by opt-out. The potential of stigma resulting from study exclusion was also appropriately minimized.

      - Based on toxicological data currently available for picaridin, coupled with appropriate exclusion criteria, study participants were unlikely to be at risk of adverse side effects with exposure.

      - Clear stopping rules and medical management procedures were in place, and no adverse events related to product exposure were reported.

      - The study was designed to minimize the likelihood of black fly bites.

   b. Voluntary and informed consent of all participants

      - The study protocol included several mechanisms designed to minimize coercive recruitment and enrollment. Monetary compensation was not so high as to unduly influence participation.

3. There were three minor protocol deviations reported, including: 1) use of a superseded data collection form; 2) The presence of a second species of biting black fly at the field test site; and 3) a gap of greater than 60 days between dose determination and field testing. The Board concluded, however, that these three deviations from the protocol were minor and did not affect the integrity of the research or the safety of participants.

Assessment of Completed Carroll-Loye Biological Research Study LNX-003: Efficacy Test of KBR 3023 (Picaridin; Icaridin) - Based Personal Insect Repellents (20% Cream and 20% Spray) with Ticks Under Laboratory Conditions.

Overview of the Study

LNX-003 was a laboratory-based study to measure the effectiveness of picaridin as a tick repellent when used in one of two compound formulations (20% picaridin KBR 3032 All-Family Insect Repellent Cream and 20% picaridin KBR 3023 All-Family Insect Repellent Spray). The efficacy of picaridin as a tick repellent was determined in a controlled laboratory setting by placing laboratory-raised, pathogen-free Western black-legged ticks (*Ixodes pacificus*) and American dog ticks (*Dermacentor variabilis*) on picaridin-treated and untreated forearms of study volunteers, and then measuring the speed and distance that moving ticks would penetrate into the treated area at 15-minute intervals. Each treated participant served as their own untreated control. Tick questing behavior was confirmed on the untreated arm of each subject before the tick was used for repellency testing.

Dosimetry data accumulated in previous CLBR studies (LNX-001 and LNX-002) were used for dose selection. For the spray product each participant received 0.97µl/cm^2 of product, equivalent to 0.9312 mg product/µl. For the cream product, the volumetric dose rate was 1.94µl/cm^2, equivalent to 1.9012 mg product/µl. For the spray product the mean picaridin dose was 100 mg per participant and 192 mg/participant for the cream product. MOE calculations were based on an assumed 70 kg subject and the acute dermal LD50 value for picaridin at the limit dose of greater than 2,000 mg/kg. For the spray product the mean picaridin dose was 100 mg per subject and 192 mg/subject for the cream product. For the cream product the MOE = 741 and for the spray product the MOE = 1429, both values exceed the target MOE = 100.

A total of 23 participants (selected from a pool of 119 volunteers diverse in age and ethnicity) participated in this study. Three were alternate participants; twenty were treated. In the test phase, ten subjects participated in each product treatment test on each day. Treatments were randomized within each gender. There were an equal number of male and female test subjects. Each volunteer participated on only one day of the test, but testing included both tick species. All ticks, repelled or not, were removed from the arm of the participant before they had time to bite. Exposure to each tick was for a period of 3 minutes on each arm. Further exposures to each species were stopped for any subject who experienced a "crossing" by that species into the treated area of the forearm confirmed by another crossing in either of the subsequent two exposure periods. This endpoint was used to calculate the CPT for each subject.

Despite an extremely long duration of testing (15.25 h), more than half the study participants did not experience a confirmed crossing. Thus, it was not possible to calculate a median time to failure for the 20% cream. Although there was also significant right-censorship of the data for the 20% spray (i.e. the actual duration of protection for participants who did not experience a confirmed crossing was not known, but was assumed to be greater than 15.25h), there were enough data points to support calculation of the Kaplan-Meier median. The 20% cream had a mean CPT = 12.6 h against *Ix. scapularis* and 15.3 h against *D. variabilis*. Most of

these data were right-censored and a median could not be calculated. For the 20% spray product, data collected with *Ix. scapularis* resulted in a median CPT of 15 h while the mean CPT equaled 14.1 h. The mean CPT against *D. variabilis* was 14 h and the median CPT was 14.1 h.

Science

Charge to the Board

Is the CLBR study LNX-003 sufficiently sound, from a scientific perspective, to be used to estimate the duration of complete protection against ticks provided by the tested repellents?

Board Response to the Charge

HSRB Recommendation

The Board concurred with the Agency's assessment (Sweeney 2010b) that this study was conducted in accordance with Good Laboratory Practices as described in 40 CFR §160, the draft EPA Guidelines §810.3700, and its own previously approved protocols and that its results provide scientifically sound data that can be used to estimate the duration of complete protection against ticks. However, the high frequency of participants for whom the repellent's protection time exceeded the long duration (15.25 hours) of the study creates statistical challenges in evaluating a specific protection time.

HSRB Detailed Recommendations and Rationale

This study (Carroll 2010b) was conducted according to the protocol previously approved by the HSRB (HSRB 2009b). The protocol fully addressed the EPA's comments in its review of the protocol and responded to HSRB comments at the meeting in October 2009. The study incorporated the results of prior dosimetry studies and lessons learned from previous laboratory tick repellent efficacy studies conducted by CLBR (Carroll 2010b). The study seems to have been carefully conducted with twenty participants (10 male and 10 female), two formulations of one repellent at the same concentration (a cream and spray, tested on separate days), and exposures to two genera of ticks (nymphal deer ticks (*Ixodes scapularis*) and nymphal American dog ticks (*Dermacentor variabilis*)) during each 15-minute interval for as long as 15.25 hours. The MOE's were very high (741 and 1429 for the cream and spray, respectively) and therefore protective of the participating volunteers. The report was clearly written and detailed.

There was interest expressed by some Board members regarding the possible influence of subjective differences in the manipulations (the "guiding" of the ticks shortly after they were placed on each participant) upon the results; however, discussion revealed that the time scale of these manipulations was sufficiently short in relation to the three minutes they were allowed to remain on the arm to not be of concern.

There was concern expressed by some Board members regarding the high rates of right censorship (especially the 60% and 80% rate in the cream formulation) caused by the lack of confirmed crossings by either tick species within the study duration (despite it lasting just over

15 hours). It was not possible to calculate a median CPT for the cream formulation using Kaplan-Meier survival analysis. The Agency may wish to consider the importance of these computations and the use of Kaplan-Meier median complete protection time and its 95% lower confidence interval when making decision regarding the efficacy of insect repellents in future studies.

Ethics

Charge to the Board

Does available information support a determination that study LNX-003 was conducted in substantial compliance with subparts K and L 40 CFR Part 26?

Board Response to the Charge

HSRB Recommendation

The Board concurred with the Agency's assessment (Carley 2010b) that the study submitted for review was conducted in substantial compliance with subparts K and L of 40 CFR 26.

HSRB Detailed Recommendations and Rationale

The document provided by CLBR (Carroll 2010b) states that the study was conducted in compliance with the requirements of the US EPA Good Laboratory Practice Regulations for Pesticide Programs (40 CFR 160); 40 CFR 26 subparts K, L and M; FIFRA § 12(a)(2)(P); and the California Code of Regulations Title 3, Section 6710. The study was reviewed and approved by a commercial human subjects review committee, IIRB, Inc. Documentation provided to the EPA indicated that IIRB, Inc. reviewed this study pursuant to the standards of the Common Rule (45 CFR Part 46, Subpart A) and found it in compliance (Carley 2010b).

1. The Board concurred with the conclusions and factual observations relating to the study, as detailed in the EPA's Ethics Review (Carley 2010b).

2. The Board concluded that this study met all applicable ethical requirements for research involving human participants, in accordance with the following criteria that had been stated in the Board's prior review of this study:

    a. *Acceptable risk-benefit ratio.* The risks to study participants were minimized appropriately and were justified by the potential societal benefits, particularly data on the efficacy of these new formulations as personal insect repellents.

        • Minors and pregnant or lactating women were excluded from participation, with pregnancy confirmed by over-the-counter pregnancy testing on the day of study or by opt-out. The potential of stigma resulting from study exclusion was also appropriately minimized.

- Based on toxicological data currently available for picaridin, coupled with appropriate exclusion criteria, study participants were unlikely to be at risk of adverse side effects with exposure.

- Clear stopping rules and medical management procedures were in place, and no adverse events related to product exposure were reported.

- The study was designed to minimize the likelihood of tick bites.

- Finally, the efficacy trial was conducted with laboratory-raised ticks free of known pathogens.

b. Voluntary and informed consent of all participants

- The study protocol included several mechanisms designed to minimize coercive recruitment and enrollment. Monetary compensation was not so high as to unduly influence participation.

Revised Agency Guidelines for Performance Testing of Topically Applied Insect Repellents (Product Performance Test Guidelines. OPPTS 810.3700: Insect Repellents to be Applied to Human Skin).

In order to improve the quality and reliability of repellent data submitted to the Agency, the EPA has developed a non-binding guidance document (Product Performance Test Guidelines. OPPTS 810.3700: Insect Repellents to be Applied to Human Skin) describing the methodology recommended by the Agency for collection of the necessary data to support registration and labeling of topically applied products (Office of Chemical Safety and Pollution Prevention 2010). These revised guidelines will replace the current "Product Performance Test Guidelines. OPPTS 810.3700: Insect Repellents for Human Skin and Outdoor Premises" released by the Agency in December 1999.

A draft version of these guidelines was first reviewed by the Board at its June 2006 meeting, and again at its October 2008 meeting (EPA HSRB 2006; EPA HSRB 2008). In these reviews the Board made many suggestions for strengthening the scientific and ethical conduct of this kind of research, and has encouraged EPA to further revise and publish its guidelines for researchers considering this type of study.

The EPA is expected to announce in the Federal Register the availability of these new draft guidelines, for immediate use for sponsors and investigators.

HSRB Evaluation

While the Board was not given a charge for consideration of the guidelines, it did have several comments to enhance the utility of the document. Specifically, the Board felt that the

document was well written and will provide sponsors and researchers with helpful guidance in the design of future efficacy tests of topically applied insect repellents. Before releasing these revised guidelines publicly, however, the Board recommended the following changes or clarifications:

1. Currently (as described in the revised Guidelines' Objectives (c)(1)(i)), the preferred measure of repellent efficacy is the duration of the CPT. CPT is important, but it is not the only (and perhaps not always the best) measure of effectiveness. A quantitative measure of the repellent's effectiveness might also be useful. For example, if opportunities to make re-applications are limited but less protection is acceptable, then consumers may wish to use a repellant with a long CPT. If the repellant can easily be re-applied however, consumers may want to choose a product with higher effectiveness. The Agency thus may want to encourage the use of study designs that yield a valid measure of repellent effectiveness and CPT. Further discussion is also needed as to the set of endpoints to present and the types of statistical analyses to be done to accurately determine repellent effectiveness and CPT.

2. The revised Guidelines strongly encourage the use of "positive [repellent] controls" (such as DEET) in the design of repellent studies (c.f. Sec. (c)(viii) in the context of scientific study design and in each of the specific guidance sections (j), (k), and (l)). The Board felt that the justification for the use of positive controls seemed weak. It was not clear from a scientific perspective just how such data would be used to interpret a given study or what value it would add, while increasing the number of additional human participants exposed to pests and the DEET control without a clear scientific benefit would raise ethical concerns. The Board thus recommended that the Agency clarify why, how and when positive controls should be included in the study design.

3. Maximum likelihood methods, as described in the Guidelines' statistical analysis section, require that the distribution of data be known. The Agency thus should remove from this section the recommendation that maximum likelihood estimates be used if this distribution is not known and the data cannot be transformed to fit an underlying distribution. Use of maximum likelihood methods would, in this case, be inappropriate.

4. The Board also recommended that, with respect to discussions of participant recruitment and vulnerability, the following changes be made:

   a. The term "race/ethnicity" should be used instead of just "race" in order to be consistent with Office of Management and Budget (OMB) categories on race and ethnicity.
   b. The Board also suggested that the EPA reexamine issues of language in recruitment and consent materials in the Guidelines, referring the Agency specifically to the Board's October 2009 report (EPA HSRB 2009b, 24), which explicitly discusses such issues of language and recommends that the Agency and study sponsors adapt the practices described in the Office of Minority Health's National Standards for Culturally and Linguistically Appropriate Services in Health (Office of Minority Health 2001). Investigators should also be urged to examine the recruitment population in advance so that speakers of other languages are present as needed.

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