March 3, 2009

Minutes of the
United States Environmental Protection Agency (EPA)
Human Studies Review Board (HSRB)
February 17, 2009 Public Teleconference Meeting
Docket Number: EPA-HQ-ORD-2009-0030

Committee Members: (See EPA HSRB Members list – Attachment A)

Date and Time:	Tuesday, February 17, 2009, 12:30 PM – 4:50 PM (Eastern Time) (See *Federal Register* Notice – Attachment B)	
Location:	via teleconference	
Purpose:	The EPA HSRB provides advice, information, and recommendations on issues related to the scientific and ethical aspects of human subjects research.	
Attendees:	Chair:	Celia B. Fisher, Ph.D.
	Vice Chair:	William S. Brimijoin, Ph.D.
	Board Members:	Alicia Carriquiry, Ph.D. Gary L. Chadwick, PharmD, MPH, CIP Janice Chambers, Ph.D., D.A.B.T. Richard Fenske, Ph.D., MPH Susan S. Fish, PharmD, MPH Dallas E. Johnson, Ph.D. Michael D. Lebowitz, Ph.D., FCCP Lois D. Lehman-Mckeeman, Ph.D. Rebecca Parkin, Ph.D., MPH Sean Philpott, Ph.D., M.Bioethics Ernest D. Prentice, Ph.D. Linda J. Young, Ph.D.
Meeting Summary:	Meeting discussions generally followed the issues and general timing as presented in the meeting Agenda (Attachment C), unless noted otherwise in these minutes.	

Introduction and Identification of Board Members

Dr. Celia Fisher (Chair, HSRB) opened the teleconference meeting with an introduction and identification of the HSRB, or Board, members participating in the call. Dr. Fisher welcomed Board members, U.S. Environmental Protection Agency (EPA or Agency) staff, and members of the public to the February 17, 2009 HSRB teleconference meeting. She

acknowledged the efforts of Dr. Paul Lewis (Designated Federal Officer [DFO], HSRB, Office of the Science Advisor [OSA], EPA) and members of EPA's Office of Pesticide Programs (OPP) in planning and preparing for this meeting.

Meeting Administrative Procedures

Dr. Lewis welcomed Board members and thanked them and his EPA colleagues for their efforts in preparing for this meeting and also welcomed members of the public. He noted that this meeting represented the first teleconference at which the Board would review a completed study. Dr. Lewis acknowledged the efforts of Mr. Hamaad Syed (OPP, EPA) for providing technical support for the teleconference and providing access to meeting documents. He introduced Dr. Daniel Strickman (USDA Agricultural Research Service), who served as a consultant on spatial/area repellents for this meeting.

As DFO, Dr. Lewis serves as liaison between the HSRB and EPA and ensures that Federal Advisory Committee Act (FACA) requirements—open meetings, timely announcements of meetings in the *Federal Register*, and meeting materials made available at a public docket—are met. As DFO, he also works with the appropriate officials to ensure that all applicable ethics regulations are satisfied. Each Board member has filed a standard government financial disclosure form that has been reviewed by Dr. Lewis and the OSA Deputy Ethics Officer in consultation with EPA's Office of General Counsel to ensure that all ethics disclosure requirements have been met. Consultants [Dr. Dan Strickman] also were briefed on conflict of interest issues. Dr. Lewis reminded participants that meeting times would be approximate and that public comments would be limited to 5 minutes.

As per FACA requirements, the meeting minutes will include descriptions of matters discussed and the conclusions reached by the Board. As the DFO, Dr. Lewis will prepare the minutes and have them certified by the HSRB Chair within 90 calendar days of the meeting. In addition, the minutes will be available at the public docket and posted on the HSRB Web site.

Welcoming Remarks

Dr. Pai-Yei Whung (Chief Scientist, OSA, EPA) welcomed Board members and thanked them for their work in preparing for the meeting. She acknowledged the efforts of the Board in contributing to the success of EPA's human subjects protection program. Dr. Whung welcomed members of the public and thanked her EPA colleagues for their efforts in preparing for the meeting.

Dr. Whung noted that during this teleconference meeting, Board members would review and offer advice on two completed studies by Carroll-Loye Biological Research. Study SPC-001 was a field study to evaluate three formulations of mosquito repellent containing picaridin. Study SPC-002 was a laboratory study that evaluated the ability of these products to repel ticks. These protocols were reviewed favorably by the Board at the October 2007 HSRB meeting. To assist the Board in its future reviews of spatial and area insect repellents, which are devices (such as citronella candles) that emit a repellent and prevent insects from entering the space, the Agency, at the request of Dr. Fisher, invited Dr. Strickman to help familiarize the Board with

technical aspects of spatial/area repellent testing. The Board will discuss various aspects of spatial/area repellent testing in part to identify necessary information to support adequate reviews of such protocols.

EPA Follow-up on Pesticide Specific HSRB Recommendations

Mr. William Jordan (OPP, EPA) noted that the protocols for the studies to be reviewed during this teleconference meeting had been favorably reviewed by the Board, the studies themselves are straightforward and well executed, and thus review of the completed studies should be uncomplicated.

Mr. Jordan offered thanks on behalf of EPA for the efforts of the Board in providing the Board report for the October 2008 HSRB meeting in a timely manner. The completed report aided decision-making by the Agricultural Handlers Exposure Task Force (AHETF). The Task Force used the report to improve the protocols it plans to submit for review at the March-April 2009 HSRB meeting. If reviewed favorably, the protocols could be executed in 2009. EPA also has made registration decisions based on Board recommendations pertaining to its review of completed repellent studies at the October 2008 meeting. In response to a question from Dr. Fisher, Mr. Jordan explained that because EPA has not yet finished certain sections of the Insect Repellent Guidelines (particularly those pertaining to statistics), the Board will not review these guidelines at the March-April 2009 meeting.

Carroll-Loye Biological Research Tick Repellent Efficacy Study (SPC-002)

Dr. Fisher reminded EPA and Board members about the statement in the October 2008 meeting that the recommendations of the HSRB are not finalized until formal Board approval of a final report is completed at a public meeting or teleconference. Board discussions held during the meeting serve as a foundation for recommendations, but do not represent a formal consensus; no consensus vote is taken at the meeting. The meeting minutes provide a summary of the meeting, but these are not approved by the Board, nor are they a substitute for the Board final consensus. Board members write their report after each meeting and integrate meeting materials and discussions into a summary of issues and recommendations. A draft report is posted for public review. The public meeting held after the public review period allows an additional opportunity to modify the draft report based on public comment and Board discussion/consensus. At the conclusion of the public meeting, the report is finalized.

Dr. Fisher thanked EPA for sending the EPA presentations prior to the teleconference meeting as previously requested. She requested that, given the advance availability of the presentation materials, EPA abbreviate its presentations during the teleconference. Mr. John Carley (OPP, EPA) explained that the tick study would be reviewed first because it was conducted first; descriptions of events occurring during the tick study would make the mosquito study somewhat easier to understand.

<u>Background and Context</u>

Mr. Carley provided an overview of completed tick repellent study SPC-002. The protocol was approved by the Independent Investigational Review Board, Inc. (IIRB) on July 17, 2007, and submitted to EPA by Carroll-Loye Biological Research in August 2007. EPA's science and ethics review of September 24, 2007 was based on the initial protocol submission. The Board reviewed this protocol favorably at its meeting on October 25, 2007. The protocol was amended in January 2008 based on review of the protocol by the HSRB as detailed in its draft final report of the October 2007 meeting; the amendments were approved by IIRB, Inc. in January 2008. The protocol also was submitted to the California Department of Pesticide Regulation (CDPR) for review and was approved as amended in March 2008. The first amendment to the protocol:

- identified the Centers for Disease Control and Prevention as the source of the ticks used in the protocol
- described pathogen screening of the ticks
- broadened the scope of the dose determination phase to include two towelette formulations
- corrected the description of the 15-percent spray with sunscreen
- clarified the extrapolation plan for other formulations
- added an efficacy data collection form
- appended the draft label for the 15-percent spray with sunscreen.

The second amendment was submitted to IIRB, Inc. in February 2008 and approved on March 6, 2008. This amendment included:

- a revised consent form (which addressed EPA concerns)
- a revised Subjects' Bill of Rights
- a revised tick handling training sheet
- an appended Materials Safety Data Sheet for the 15-percent spray with sunscreen
- a treatment allocation form
- a revised tick crossing data capture form
- a table to clarify the extrapolation plan.

Dose determination for SPC-001 and SPC-002 was executed under SPC-002 and shared by both protocols. Dose determination took place March 15-19, 2008. Efficacy testing for SPC-002 was conducted March 22-23, 2008. A deviation regarding the use of limb measurements from previous studies was reported to IIRB, Inc. on July 6, 2008. IIRB, Inc. accepted the deviation report on July 14, 2008. The study report was completed on August 19, 2008. The primary submission of the report to EPA occurred on September 9, 2008, and a supplemental submission was made on November 7, 2008.

<u>EPA Science Assessment of Carroll-Loye Biological Research Tick Repellent Efficacy Study (SPC-002)</u>

Mr. Kevin Sweeney (OPP, EPA) provided EPA's science review of SPC-002. The objective of this protocol was to test five repellent formulations containing picaridin for the ability to repel ticks in a laboratory setting. Each test used two species of ticks, which were

tested in the nymphal stage because these ticks are most likely to harbor disease-causing pathogens. Efficacy was reported as Complete Protection Time (CPT).

Dose determination was performed to estimate typical consumer dosing behavior for the five repellent formulations. These were a 5.75-percent towelette (121-90), a 7-percent pump spray (121-89), a 12-percent towelette (121-93), a 15-percent pump spray (121-91), and a 15-percent pump spray with sunscreen (121-OT). The dosimetry phase included 10 subjects and established a typical consumer dose for each of the five formulations; however, the towelette formulations were excluded from the testing phase. The lower mean dose for each pair of "equivalent liquid formulations" was selected for use in efficacy testing. Typical arm doses determined for equivalent liquid formulations (grand mean dose) were 1.38 ± 0.40 milligrams per square centimeter (mg/cm^2) for the 5.75-percent towelette, 0.59 ± 0.32 mg/cm^2 for the 7-percent pump spray, 1.26 ± 0.42 mg/cm^2 for the 12-percent towelette, and 0.93 ± 0.50 mg/cm^2 for the 15-percent pump spray. Leg doses determined for the mosquito repellency testing were lower than those for the arm. Only three of the products (the 7-percent pump spray, 15-percent pump spray, and 15-percent pump spray with sunscreen) were used in efficacy testing. The standard dose rates for these products for arms and legs were 0.59 mg/cm^2 and 0.48 mg/cm^2 for the 7-percent pump spray; 0.93 mg/cm^2 and 0.65 mg/cm^2 for the 15-percent pump spray; and 0.75 mg/cm^2 and 0.46 mg/cm^2 for the 15-percent pump spray with sunscreen, respectively.

The three pump spray formulations were tested to determine CPT in the laboratory against two species of nymphal ticks to satisfy a condition of registration imposed by EPA. To execute this protocol, 30 subjects were trained in the laboratory to handle laboratory-reared, pathogen-free ticks and to remove them before they could bite and bury. Ten subjects were treated on the arms with each test material. The treatments were not distinguishable from each other and neither subjects nor technicians recording the results knew who received which treatment. Fifteen subjects were tested on each of two successive days. The untreated arm of each treated subject served as a control to ensure that only actively questing ticks were used in efficacy testing. Each subject tested one nymphal tick of each species in each 15-minute exposure period until efficacy failure or approximately 15 hours post-treatment. CPT was calculated as the mean time from treatment to "First Confirmed Crossing" or FCC, e.g., the time at which a tick first crossed into the treated area on the subject's arm.

Standard doses determined during dosimetry testing were applied to subjects' forearms. Using a standard 70-kilogram (kg) body weight to determine the dose rates (milligrams per kg [mg/kg]), Margins of Exposure (MOEs) for each formulation were 6,623 (7-percent pump spray), 1,881 (15-percent pump spray), and 2,265 (15-percent pump spray with sunscreen). These exceed the target MOE of 100, so risk to subjects was low.

There was considerable variability in the test results and some right censoring of data for the products containing 15 percent picaridin. Mean CPT and standard deviation for testing using *Ixodes scapularis* were 7.9 ± 1.4 hours for the 7-percent pump spray, 11.8 ± 3.3 hours for the 15-percent pump spray, and 8.7 ± 4.3 hours for the 15-percent spray with sunscreen. For testing using *Dermacentor variabilis*, mean CPTs and standard deviations were 5.7 ± 2.1 hours for the 7-percent pump spray, 9.7 ± 4.0 hours for the 15-percent pump spray, and 8.2 ± 4.9 hours for the 15-percent spray with sunscreen.

The primary protocol deviation occurring for this study was the use of some subject limb measurements on file from previous studies. The same deviation was reported for protocol LNX-001, which was reviewed by the HSRB in October 2008. The deviation was reported to and accepted by IIRB, Inc., and did not affect the scientific integrity of the study or the results. In response to comments from EPA, the "lotion" product was more completely characterized in the protocol, the source of ticks was identified, and steps taken to ensure that the ticks were disease free were described. In response to the HSRB, the protocol clarified that subject allocation to treatments would ensure that no subjects tested more than one repellent to ensure consistency with the stated statistical design.

EPA has found that the study provides scientifically valid results that meet Agency standards. For purposes of labeling, the data are adequate to support the following claims of tick repellency: 7 hours for the 7-percent spray (product 121-89 Cutter Insect Repellent 7K), 11 hours for the 15-percent spray (product 121-91 Cutter Insect Repellent 15 KP), and 8 hours for the 15-percent spray with sunscreen (product 121-OT Cutter Insect Repellent SS).

Clarifying Questions

Dr. Linda Young opened the discussion by stating that, in her opinion, the data do not support the label claims proposed by EPA. Dr. Janice Chambers commented that this was a policy issue outside the Board's purview, but Dr. Fisher countered that although EPA decides how to use the data for labeling decisions, the Board has the responsibility to advise on whether the data are sufficient to support CPT claims that will be included on the label.

Dr. Young complimented EPA for clearly describing the research objective for this protocol. Study design, analysis, and data interpretation all are created based on the research objective; however, Dr. Young expressed concern that any one study of an insect repellent could suffice for label information that will be used on a nationally marketed product. Diverse mosquito, tick, and human populations exist across the United States as do differences in the susceptibility of species to repellents and attractiveness of humans to insects. The results from the tick protocol show mean protection times of less than 7 hours for one of the two species; therefore, the EPA label claims that were included in the materials sent to the Board are inconsistent with study results. This protection time is within the confidence interval, but taking protection time from the lower band of the confidence interval would account for most resistant species. In addition, if the time at first bite was reported, rather than the second confirming bite, which would result in a CPT closer to 3 hours. Mean protection time is not equal to CPT and the uncertainty inherent to these observations should be conveyed to the consumer. The public has become increasingly literate in matters related to statistics and probability and should be provided with margin of error information.

Dr. Fisher explained that the Board must make two decisions related to the completed study: (1) whether the investigator followed HSRB recommendations related to the study design and data collection, and whether the data were reliably collected; and (2) whether there are limitations to the use of the data for its intended purpose as stated in conclusions by EPA. In 2008, the Board decided that CPT was inappropriate for right-censored data and EPA should not

rely on this measure for judging efficacy. During this teleconference, the Board was provided with additional information related to the way that EPA interprets and uses the data and thus the Board should comment on this issue.

Dr. Young agreed that there were no marked departures from the approved protocol; however, the data do not support the claims made by EPA. Dr. Stephen Brimijoin stated that the Board was confusing policy decisions with scientific determinations. He agreed with Dr. Young's statements regarding matching study design to study objective and being aware of how the data will be used; however, he disagreed that the protocol was flawed because it was not performed using more insect species, more field sites, and much larger numbers and diversity of subjects. He remarked that he would not agree with a decision stating that the data are not sufficiently scientifically sound to be relied on by EPA. This would be inappropriate, particularly given the efforts of EPA and Carroll-Loye Biological Research to address issues raised by the Board concerning these matters. He agreed with Dr. Young that the studies were not designed to produce a CPT of 7 hours, and that an absolute CPT of 7 hours was invalid. The Board charge question asks if the data are scientifically sound to be used for the intended purpose. These data will be used to devise a label; the Board can recommend that the label refer to the variability and error inherent in this measure; however, the Board must focus on whether the data are scientifically sound.

Dr. Michael Lebowitz suggested that there was confusion between the Board charge question and EPA conclusions. The Board charge pertains only to the scientific soundness of the data. The conclusions presented by Mr. Sweeney refer to how EPA would use the data if the Board agrees that the data are sound. The Board can answer the charge question and then respond to EPA conclusions presented in the SPC-002 presentation as an advisory note stating that the data could be more appropriately used.

Dr. Alicia Carriquiry agreed with Dr. Young's opinion that the label claims for CPT were too optimistic. In addition, it is unclear whether these laboratory results can be applied to the entire United States. It is unlikely that the participants were diverse enough to support application of the results to all people in the United States and to all tick species. The Board should consider whether the data are sufficiently scientifically sound to be extrapolated to the entire country.

Dr. Fisher asked why tick repellency was studied under laboratory conditions. Mr. Sweeney answered that tick studies are not performed in the field because of the diseases carried by ticks and the likelihood that a participant would not notice a tick bite in the field. Dr. Dallas Johnson requested clarification on the use of mean crossings per subject to determine CPT. Mr. Sweeney explained that lines are drawn on the participants' arms and ticks are observed to determine when they cross the lines. A confirmed crossing requires the initial crossing to be confirmed by another crossing within 15 minutes; this indicates product failure.

Dr. Fisher noted that the use of limb measurements taken previously seems to have occurred several times. Mr. Carley clarified that this protocol deviation occurred for the first time when the tick protocol was conducted in March 2008. In October 2008, the Board reviewed a study conducted in June 2008. The episode was noted in the summer 2008; two mosquito and

one tick protocol were conducted at the same time using the same methods. The protocol deviation discussed at the October 2008 HSRB meeting is the same occurrence reported during this discussion of the completed protocol.

EPA Ethics Assessment of Carroll-Loye Biological Research Tick Repellent Efficacy Study (SPC-002)

Mr. Carley provided EPA's ethics review of SPC-002. EPA found this study to be well conducted and designed and it was modified to incorporate HSRB and EPA recommendations. One protocol deviation occurred, namely the use of previously recorded limb measurements for some subjects. This deviation was unintentional, reported to the IIRB, Inc. in a timely manner, and had no ethical consequences.

In its September 24, 2007 review of SPC-002, EPA asked the investigator to incorporate an appropriate data collection form for recording efficacy test results; this was addressed in Amendment 1 and refined in Amendment 2. EPA also requested inclusion of product labels in the protocol and that the labels be provided to subjects during the dose determination phase. A draft label for the 15-percent spray with sunscreen thus was attached to the protocol via Amendment 1. EPA asked that the investigator address in the consent form the risk of tick bites and diseases and measures taken to prevent bites; these issues were addressed in the consent form revisions provided with Amendment 2. In its March 6, 2008 report, the HSRB had no additional recommendations for refinements to this protocol.

EPA has found that SPC-002 meets the applicable standards, namely 40 Code of Federal Regulations (CFR) § 26.1303, 26.1703, 26.1705, and Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) §12(a)(2)(P). The requirements of 40 CFR § 26.1303 to document the ethical conduct of SPC-002 were met in the supplemental submission of November 7, 2008. SPC-002 did not involve intentional exposure of pregnant or nursing women or of children less than 18 years of age. The only protocol deviation was unintentional, promptly reported, and of no ethical significance. The subjects were fully informed and participated voluntarily. SPC-002 thus was conducted in substantial compliance with the requirements of 40 CFR part 26, subparts A-L. Assuming SPC-002 is determined to be scientifically acceptable; EPA finds no limitations in law or regulation to reliance on it in actions under FIFRA.

Charge Questions

The Board was asked to consider whether SPC-002 was sufficiently sound, from an ethical perspective, to be used to assess the repellent efficacy against ticks for the three formulations tested. The Board also was asked to address whether the available information supports a determination that the study was conducted in substantial compliance with subparts K and L of 40 CFR part 26.

Public Comments

Dr. Scott Carroll, on behalf of Carroll-Loye Biological Research

Dr. Scott Carroll acknowledged that the Board's concerns regarding statistical analysis and interpretation of the data and how EPA uses the data have been persistent issues. He explained that the studies conducted by Carroll-Loye Biological Research are more thorough and incorporate much larger sample sizes compared to prior work. The reliability of the data also has been improved. He agreed that in other fields, experiments involving human subjects have much larger sample sizes; however, work in the field of medical entomology has a history of obtaining reliable results with relatively small sample sizes. DEET labeling, for example, is remarkably accurate. Dr. Carroll also informed the Board that a Carroll-Loye Biological Research protocol was recently published in the *Journal of Medical Entomology*, thus demonstrating that this work meets peer review standards. He expressed appreciation for the Board's input on various Carroll-Loye Biological Research protocols and stated that he will continue to work to improve these studies.

Dr. Brimijoin noted that laboratory research protocols often are repeated a number of times, but that this might be more difficult when the work is being performed in the field or for a commercial entity to support labeling requirements. He commented that the costs of experimentally addressing all Board concerns related to multiple species, different field conditions, and diverse human populations, would likely be prohibitive.

Dr. Fisher remarked that her impression is that picaridin was safer than DEET, but DEET was a more effective repellent; however, DEET protection times appear to be lower than those obtained in the picaridin studies. Dr. Carroll agreed that picaridin appears to be safer than DEET, but there is no evidence that it is less effective. The published literature on picaridin indicates that it is slightly to moderately more effective than DEET. Dr. Fisher stated that the CPT for picaridin appeared to be twice as long as that for DEET. Dr. Carroll commented that CPT will vary because of differences in studies with respect to insect species and subjects. Picaridin also is known to be more effective against *Anopheles* sp. than DEET. Dr. Fisher noted that data from a large number of studies should be considered before making strong statements regarding the relative effectiveness of these products.

Board Discussion

Scientific Considerations – Study SPC-002

Dr. Chambers opened the science discussion for SPC-002. She noted that the label for the pump spray with sunscreen will indicate 5 hours of protection time, not 8 hours. She stated that the study was scientifically valid. The protocol was clearly written, and the deviation, which was done to reduce inconvenience to participants, had no impact on data quality. The data are scientifically valid and the study accomplished its objective. Labeling decisions made by EPA are beyond the purview of the Board.

Dr. Carriquiry agreed that the protocol was followed, but the data do not support the label claims made by EPA, which also could be considered an objective of the study. It is difficult to determine whether the study is scientifically valid in the absence of a clear objective. If the data are to be used for developing a label, the label should include caveats related to the lack of

generalizability of the data. Dr. Carriquiry disagreed with the conclusions drawn by EPA regarding the protection times it developed based on the data.

Dr. Fisher reminded Board members that they should assess the protocol based on whether execution of the study followed the protocol, the data were reliably collected, and whether statistical analyses were appropriate and sufficient with respect to EPA's conclusions. Board members agreed that the execution of the study followed the protocol and that the data were reliably collected.

Dr. Carriquiry agreed that the statistical analyses were correctly executed, but there were problems with the interpretation of the analyses results. Dr. Johnson noted that this was not the first meeting at which the Board had been presented with EPA conclusions regarding the use of the data to establish protection times for a label and suggested disregarding this information. Dr. Fisher responded that the Board has often asked EPA to provide information on how it will use data from these protocols to inform labels. EPA is drawing conclusions that the study sufficiently addresses product protection time and no further studies are needed. Dr. Johnson stated that if EPA wishes the Board to address its use of the data for labels, this should be included in the Board's charge questions.

Dr. Lois Lehman-Mckeeman stated that the experiment was reasonably well-conducted and had been improved; however, the conclusions were somewhat puzzling. She agreed with Dr. Chambers regarding the purview of the Board for determining appropriate use of the data by EPA. The Board has previously assessed data without knowing how EPA intended to use the data. She indicated that she was reluctant to conclude that the study could not be used because of the Board's disagreement with EPA conclusions. Dr. Brimijoin agreed with Dr. Lehman-Mckeeman and noted that the Board has previously concluded that if a study is not scientifically valid, it is not ethically valid and the data cannot be used by EPA. In his opinion, finding that a study is not scientifically valid should be reserved for studies with serious flaws. He encouraged Board members with reservations about the statistical analyses and designs of the protocols to state their reservations for the record and offer advice; however, the Board must conclude that SPC-002 is scientifically valid and that EPA can use the data.

Dr. Fisher, drawing on the Board's October 2008 written report on these protocols, reminded the Board that it had approved the study design, but was troubled by and noted in the report the lack of generalizability of the data. Recommending that generalizability be improved is not inconsistent with approving the conduct of the study. She agreed that the study was well conducted and provided reliable data, but the data are useable only in a limited sense.

Drs. Chambers and Lebowitz recommended that the Board find the study scientifically valid as conducted. Dr. Fisher asked whether the Board would address the EPA conclusions. Dr. Brimijoin responded that the Board was not asked to address this issue and that he would not agree to any conclusion other than that the study was valid. Dr. Fisher disagreed that the data from the study was adequate to support the specific protection times presented in the EPA's conclusions. Dr. Chambers noted that the conclusions were not drawn by those conducting the study and were not part of the study. Dr. Lewis suggested that these concerns be included in the Board's response to the charge questions in its report.

Ethical Considerations – Study SPC-002

Dr. Sean Philpott opened the ethics discussion by noting that the study meets the applicable ethical requirements. There is an acceptable balance of risks and benefits, participation was voluntary, informed consent was obtained, and justice issues were addressed. The risks to the subjects were minimal and justified by the potential societal benefits of marketing new tick repellent formulations. He commended Dr. Carroll's respect for subject privacy regarding possible unexpected results of pregnancy tests by using alternate subjects. The study had clear medical stopping rules, the risk of tick bites was low, and pathogen-free ticks were used. The protocol was designed to ensure voluntary informed consent and mechanisms to avoid coercion were in place.

The protocol deviation that was reported occurred when a laboratory manager acted on EPA's suggestion for using archived measurements. The manager used archived measurements without consulting Dr. Carroll or IIRB, Inc. Dr. Carroll has acknowledged that this was a result of a communication error and has assured EPA and the Board that it will not happen again. The deviation posed no increase in risk to the study participants and thus is not a serious issue. Dr. Philpott concluded by stating that the study was ethically conducted and EPA therefore can use the data generated by it. Dr. Ernest Prentice agreed with Dr. Philpott's conclusions. SPC-002 was conducted in compliance with 40 CFR subparts K and L. He expressed some concern about the statistical analyses and EPA conclusions regarding these data, but agreed that these matters should be discussed at the next Board meeting; however, he concluded that the study was well conducted and the data can be used by EPA. Dr. Susan Fish agreed with Drs. Philpott and Prentice.

Dr. Fisher summarized that the study was well conducted and generated the appropriate data. She recommended that the Board note in its report the importance of addressing issues raised at this meeting at the next Board meeting, particularly statistical matters broached by Drs. Carriquiry and Young.

Carroll-Loye Biological Research Mosquito Repellent Efficacy Study (SPC-001)

Background

Mr. Carley provided an overview of the mosquito repellent efficacy study SPC-001. This study underwent the same EPA and HSRB protocol review process as SPC-002, with some differences in the amendment process. SPC-001 was submitted to CDPR and then amended in mid-May 2008 after comments were received from CDPR and the HSRB. Final CDPR approval was received on May 29, 2008. The first amendment to the protocol was similar to that for SPC-002, including adding dose determination for the two towelette formulations, correcting the description of the 15-percent pump spray with sunscreen product, clarifying the extrapolation plan, and clarifying allocation of subjects to treatments. Amendment 2 clarified terminology and language, added a table to further clarify the extrapolation plan, further clarified allocation of subjects to treatments, clarified timing of pregnancy testing, and updated the demographic description of the pool from which subjects were recruited. Field testing for SPC-001 was

conducted June 8-14, 2008. The deviation report to IIRB, Inc. regarding the use of limb measurements from previous studies was submitted on July 6, 2008.

EPA Science Assessment of Carroll-Loye Biological Research Mosquito Repellent Efficacy Study (SPC-001)

Mr. Sweeney provided EPA's review of the science of SPC-001. The dose determination phase for this study was shared with that for SPC-002. The objectives of this study were to measure CPT in the field against mosquitoes for three repellent formulations containing picaridin: 7-percent pump spray (121-89), 15-percent pump spray (121-91), and 15-percent pump spray with sunscreen (121-OT). This study was performed to satisfy a condition of registration imposed by EPA.

This study was similar to other recent Carroll-Loye Biological Research field studies. Subjects were trained in the laboratory to aspirate landing mosquitoes before they bite. Laboratory-reared, pathogen-free mosquitoes were used. Neither subjects nor technicians recording results knew who received which product. Untreated subjects were used to monitor mosquito pressure; each subject was attended by two technicians to aspirate landing mosquitoes. The study involved 10 subjects treated with one of the three tested formulations and 2 untreated control subjects who participated in each of 2 field trials; some subjects participated on both days. Both treated and untreated subjects were exposed to mosquitoes for 1 minute at 15-minutes intervals, until efficacy failure or up to 17 hours post-treatment. CPT was calculated as the mean time from treatment to "First Confirmed Landing with intent to bite" or FCLibe.

Standard doses were applied to subjects' arms and legs and a standard 70-kg body weight was used to determine the dose rates. The MOEs for arms were the same as for SPC-002. The MOEs for legs were 3,597 (7-percent pump spray), 1,197 (15-percent pump spray), and 1,682 (15-percent pump spray with sunscreen). Since these are in excess of the target MOE of 100, risk to subjects was low.

The field sites used were located in the California Central Valley. Site 1 was located in Butte County and was a grassy lakeside with shrubs. Site 2 was located in Glenn County and was a tall native forest understory. Various *Aedes* and *Anopheles* sp. were present at the sites, as was *Culex tarsalis*. The investigator ensured that neither West Nile Virus (WNV) nor other pathogens had been detected at the sites by various monitoring agencies.

The median CPT values were close to the mean CPT values and the variability was not as great as in SPC-002. Mean CPT and standard deviations at Site 1 were 8.4 ± 2.1 hours for the 7-percent spray, 10.1 ± 4.0 hours for the 15-percent spray, and 12.7 ± 4.9 hours for the 15-percent spray with sunscreen. At Site 2, mean CPTs and standard deviations were 7.0 ± 2.2 hours for the 7-percent spray, 10.7 ± 0.8 hours for the 15-percent spray, and 10.9 ± 0.8 hours for the 15-percent spray with sunscreen.

The deviation reported for study LNX-001 and SPC-002 regarding the use of subject limb measurements on file from previous studies was reported for this protocol. The deviation was reported to and accepted by IIRB, Inc. The deviation did not affect the scientific integrity or

the results of the study. In response to a comment in the EPA review, the investigator added a more thorough description of the 15-percent pump spray with sunscreen to the protocol through Amendment 1.

EPA has concluded that the study provides scientifically valid results that meet EPA standards. For purposes of labeling, this study supports claims of repellency of 8 hours for the 7-percent spray (product 121-89), 10 hours for the 15-percent spray (product 121-91), and 12 hours for the 15-percent spray with sunscreen (product 121-OT).

EPA Ethics Assessment of Carroll-Loye Biological Research Mosquito Repellent Efficacy Study (SPC-001)

Mr. Carley provided EPA's review of the ethics of protocol SPC-001. The study was well designed, executed properly, and clearly reported. The submission of the report of the completed study meets regulatory standards for completeness. The same protocol deviation in protocol SPC-002 (use of previously recorded limb measurements) was properly reported to IIRB, Inc. and was of no ethical consequence. In response to EPA and the HSRB ethics reviews, the investigator incorporated an appropriate data collection form for recording field test results, and provided product labels in the protocol and to subjects during the dose determination phase. In its March 6, 2008 report on its review of this protocol, the HSRB made no additional recommendations for refinements.

The applicable standards for this protocol are 40 CFR § 26.1303, 26.1703, 26.1705, and FIFRA §12(a)(2)(P). The investigator documented the ethical conduct of SPC-001 as required. SPC-001 did not involve intentional exposure of pregnant or nursing women or of children less than 18 years of age. The only protocol deviation (which was unintentional) was reported promptly and was of no ethical significance. Subjects were fully informed and participated voluntarily. SPC-001 was conducted in substantial compliance with the requirements of 40 CFR part 26, subparts A-L. Assuming SPC-001 is determined to be scientifically acceptable, EPA finds no barrier in law or regulation to the Agency's reliance on it in actions under FIFRA.

Charge Questions

The Board was asked to consider whether SPC-001 was sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy against mosquitoes for the three formulations tested. The Board also was asked to address whether the available information supports a determination that the study was conducted in substantial compliance with subparts K and L of 40 CFR part 26.

Public Comments

Dr. Scott Carroll, on behalf of Carroll-Loye Biological Research

Dr. Scott Carroll offered to respond to questions from the Board. No comments were provided.

Board Discussion

Scientific Considerations – Study SPC-001

Dr. Chambers opened the science review by stating that her opinion of this protocol was the same as that for SPC-002. The report was clear, the study was well conducted, the MOE was acceptably high; therefore, the study is scientifically sound. Dr. Carriquiry agreed that the study was well conducted, the data are valid, and the analyses were correct; however, she remarked that EPA had overstated its conclusions. The Agency's presentation indicated the median CPT to be slightly longer than the mean, which implies that the distribution of CPTs is not symmetric. This suggests that the mean is probably not the best value to use when making label recommendations. In response to a question from Dr. Fisher, Dr. Carriquiry agreed that this implied limitations to conclusions drawn about protection times. Dr. Lehman-Mckeeman agreed with Dr. Chambers' assessment.

Dr. Fisher summarized that the Board consensus was that the study had been conducted according to the protocol and the data were reliably collected, but that some Board members concluded there were statistical limitations to the generalizability of the data. She also noted that the Board did not wish to discourage EPA from seeking the Board's advice on how data from completed protocols might contribute to the Agency's labeling decisions, especially since this information provided a context within which to better judge the adequacy of the data for the Agency's needs. However, the Board viewed the current language of the charge questions as potentially limiting the scope of its recommendations. Further general discussion at the next face-to-face Board meeting regarding the wording of the charges was suggested.

Ethical Considerations – Study SPC-001

Dr. Philpott opened the ethics review by noting that the study was similar to SPC-002. Given the available information, SPC-001 is in substantial compliance with the pertinent regulations. The main difference between this study and SPC-002 is the conduct of SPC-001 in the field rather than laboratory and in its study of efficacy against mosquitoes rather than ticks. Appropriate stopping rules were used and medical assistance was available. Although field testing is accompanied by possible exposure to vector-borne diseases, the studies were conducted at sites at which neither WNV nor other pathogens had been detected for at least 1 month prior to the study. Molecular analyses of mosquitoes captured during the study showed that no pathogens were present. Follow-up with the participants found no adverse effects attributable to pathogens or to the products themselves. Dr. Philpott concluded that the data could be used by EPA. Drs. Fish and Prentice agreed with Dr. Philpott's review. Dr. Fisher concluded that the Board consensus was that SPC-001 had been ethically conducted.

Spatial/Area Insect Repellent Testing

Introduction

Dr. Fisher explained that because the HSRB will for the first time review protocols for spatial repellent testing at a future HSRB meeting, the Board needs to be educated about such

protocols. A working group was created that generated a list of questions for EPA concerning these protocols. In response, EPA asked Dr. Dan Strickman to serve as consultant to the Board and address these questions. Both Dr. Strickman and EPA addressed the questions posed by the Board working group and provided guidelines and other useful information. Drs. Fisher and Lewis also targeted additional areas to address. EPA did not orally present information from the meeting materials; however, Dr. Strickman provided a review of spatial/area insect repellent testing and addressed some issues raised by the Board.

Technical Aspects of Spatial/Area Repellent Testing

Dr. Strickman described differences between testing spatial/area repellents versus topical repellents. Topical repellants operate at the last stages of the biting process and are highly targeted to protect subjects. Spatial repellents exert their effects on the insect at a distance from the subject, and these effects are different than those of topical repellants. This category of repellents includes devices that emit repellent chemicals and also physical barriers, such as bed nets and screened suits.

Spatial repellent testing often uses a human "surrogate," such as a carbon dioxide-baited trap. Spatial repellents function by stopping insect movement through irritating, intoxicating, or killing the insect before it reaches a human; therefore, determining the proportion of insects whose movements are stopped before reaching the trap can be used to test efficacy, rather than counting numbers of landings or bites. However, if the spatial repellent works by interfering with mechanisms involved in attraction of insects to humans, humans must be used in testing.

Complete protection time is not appropriate as a measure of efficacy for spatial repellents because spatial repellents do not offer 100-percent protection. Duration of effect and percent efficacy are used instead; for example, a spatial repellent may be characterized as reducing bites by 60 percent for up to 2 hours. The percent effectiveness should not vary over time for emitting devices. Once the device has emitted the targeted dose of chemical, effectiveness should remain the same until the device stops emitting.

Spatial repellent devices are often tested under controlled conditions to avoid confounding effects of wind. These tests are performed in large, house-sized cages, which allow testing to be conducted at any site within the United States and allow investigators to choose which insect species to test. Because of variables, such as the presence of various species and, especially, wind, it is essentially impossible to gather truly representative data in the field.

Clarifying Questions

Dr. Johnson asked how cage studies were used to judge efficacy of a spatial repellent. Dr. Strickman explained that the use of cages allows investigators to pre-determine the number of mosquitoes present, which permits determination of a true measure of protection. This approach also avoids the use of human subjects. An emitting device can be placed in a large cage between the mosquito release point and a trap, and the number of mosquitoes that travel through the emitted repellent to the trap can be counted. Dr. Fisher asked whether the lack of human subjects meant that the effect of differences in attractiveness to mosquitoes on repellent

efficacy could not be judged. Dr. Strickman explained that this depends on the mode of action of the device. Most devices emit a pyrethroid chemical that is emitted as small particles and gas vapors. Most mosquitoes do not pass through the cloud because it is irritating, although those that do enter the cloud become immobilized and do not bite. In this case, the ability of the device to stop mosquito movement is being tested, rather than its effect on mosquito-human interactions. In contrast, human subjects would be needed to test devices that emit compounds that block mosquito receptors to human attractants. These do not stop mosquito movement, but instead render the mosquitoes unable to detect humans. Dr. Fisher inquired if such studies would involve use of protective clothing. Dr. Strickman responded that protective clothing that allows odor and heat to escape can be used, but problems arise with catching the mosquitoes to determine the number that are not affected by the blocking compound. An assistant could aspirate landing mosquitoes, but this approach is not standardized. Bed nets with reverse funnels that prevent a connection with the net interior also could be used to catch mosquitoes as they seek the host.

Dr. Johnson questioned how experimental results would be extrapolated to real-life conditions. Dr. Strickman replied that a study that compared the number of bites received in the presence and absence of the device could be performed. Although this approach might be more accurate, determining the percentage protection over time by monitoring mosquito movement is considered accurate and avoids exposing human subjects to mosquito bites. Dr. Strickman acknowledged that effectiveness under laboratory conditions differs from real-life effectiveness. For example, a 50-percent reduction in bites might seem impressive in a controlled situation, but would not satisfy the consumer. Dr. Fisher inquired if labels for these products indicated protection as percent reduction in bites. Dr. Strickman explained that EPA decides how this information is conveyed on the label. Dr. Strickman added that current spatial/area repellents are not 100-percent effective.

Dr. Carriquiry noted that, when extrapolating from a controlled study to real-life conditions, a number of assumptions must be made. Wind is likely to be a significant factor affecting efficacy, but is not a factor under controlled conditions. She asked if these products were tested under controlled conditions to permit comparison between products. Dr. Strickman answered that performing the tests under controlled conditions does allow comparison to be made. It might be possible to generate laminar flow of a specific speed for the tests, but not including wind provides a more straightforward approach. Dr. Carriquiry inquired if wind should be incorporated into the tests because it does not affect all products the same way. Dr. Strickman acknowledged that the public might prefer a more accurate measure of protection under real-life conditions, but it is not realistic to gather all the information that would be needed to do so. Variations among people, including use of sunscreen or deodorant, and variations among mosquito species are vast. The controlled tests are primarily used to compare products and determine if one product offers better protection than another under controlled conditions. Dr. Johnson questioned if the Board would review studies that compare products or studies that are used to make a protection claim. Mr. Sweeney explained that the products make protection claims, but the claims are often compared across products; thus, similar test conditions that offer better comparison are needed. Dr. Fisher inquired how, given that labels are used to provide relative information for the consumer, EPA ensures that the data are consistent and collected

under consistent conditions. Mr. Sweeney replied that the Agency offers guidance on data use and also has established study requirements.

Dr. Fisher explained that Board members had been assigned to discuss questions that will arise when the HSRB evaluates spatial/area repellent studies; these questions also will serve to provide EPA with an overview of Board concerns and will allow sponsors to learn how the Board has been educated in matters related to these types of studies, which should help them tailor their protocols. This discussion also was designed to help the Board develop criteria for assessing scientific validity of such studies when presented to the Board.

Public Comments

Dr. Fisher invited oral public comment on spatial/area repellent testing. No oral public comments were presented.

Board Discussion

Environmental Aspects

Dr. Lebowitz opened the discussion by noting that many studies of spatial/area repellents do not involve humans and thus will not be reviewed by the Board. Significant differences in the behavior of repellents under different conditions, or in the presence of different insect species or individuals exist and will affect efficacy. It is difficult to test these variables because there is little existing data from work performed under controlled conditions that tests the effects of laminar flow, turbulence, temperature, humidity, and other factors to allow extrapolation of repellent efficacy under controlled conditions to real-life situations. He acknowledged that the amount of testing that would be required to account for all possible environmental conditions is unrealistically large. Thus, Dr. Lebowitz recommended that better protocol guidelines be established, or that the Board recommend that EPA develop more rigorous standards for testing these repellents to improve comparisons among different repellents. The mode of application and the kind of chemical used also will be important for comparing efficacy tests. Dr. Lebowitz noted that certain kinds of emitters, such as candles and coils, may have health effects; therefore, proper determination of MOEs is crucial. He recommended that the Board draft a report of their concerns related to spatial/area repellent testing and provide it to Dr. Strickman and EPA for review.

Dr. Richard Fenske agreed that much of the testing of these repellents will not be reviewed by the HSRB, because the tests do not involve humans. He also agreed that excluding humans from testing will allow flexibility for more experimental scenarios, but some repellents, such as those that affect human attractiveness for insects, will require human testing. Dr. Fisher stated that although the Board will not review studies that do not involve humans, the Board may need to consider why humans are included in a study and whether this is appropriate. She added that the Board should consider whether studies that include humans are likely to generate data that will result in labeling that offers greater protection for humans. The HSRB's charge is to consider whether testing in human subjects is necessary or needed to provide the best possible information for the consumer. Dr. Lebowitz agreed that scenarios may exist in which

human testing is desirable, but a series of cage experiments or use of sentinel species may be safer and adequate. He stated that the Board may not have sufficient experience with this type of testing to determine when human testing is needed. There is a great deal of variability across studies of spatial/area repellent testing and thus it is difficult to determine the most appropriate type of testing.

Study Design

Dr. Lehman-Mckeeman opened discussion of study design by stating that because the Board will review a number of different kinds of devices and products, all protocols must include a clear description of the product, the compound it delivers, and how the product delivers the compound. Protocols should include specific details concerning how devices will be operated and how correct operation will be determined. She agreed that justification of the inclusions of humans in such studies will be needed. Standards also should be established. For example, if testing is conducted outdoors, minimal acceptable criteria for allowable environmental conditions are needed; these might cover a range of acceptable conditions. Dr. Fisher suggested that the Board also may wish to be educated about the need for field testing versus testing in a controlled setting.

Dr. Lehman-Mckeeman commented that design or measurement standards for dispensing devices should be explained. Determination of the ambient concentration of the active ingredient should occur during testing to determine whether the device functioned properly and to calculate MOE. Regarding dosimetry data, physical and chemical characteristics of the active ingredient for any volatile product will need to be specified because these characteristics will determine how the active ingredient permeates the space. The Board also will need to understand parameters such as skin penetration and inhalation exposure related to the active ingredient. Physical devices with non-adjustable discharge rates could be tested under laboratory conditions to determine the time of discharge and chemical duration in the environment after completion of discharge; these matters should be specified in the protocol. In response to a question from Dr. Fisher, Dr. Strickman explained that chemical release by repellent emitters is usually expressed as ambient concentration. Dr. Lehman-Mckeeman remarked that determining ambient concentration should be based on formulation, because formulation could alter the behavior of the active ingredient.

Dr. Lehman-Mckeeman concluded by stating that standardization of a testing paradigm for spatial/area repellents is needed. Devices that discharge a compound will differ from products such as candles that emit a repellent. Physical and chemical properties of all formulations will need to be known.

Dr. Brimijoin agreed with Dr. Lehman-Mckeeman's conclusions. He commented that given the apparent mismatch between study design and study objective (informing labeling practice) in the topical repellent studies, sponsors of spatial/area repellent studies should be aware of this issue and its importance to the Board. He agreed that specific justification of the use of humans in spatial/area repellent testing will be needed. It is not always ethically more defensible to perform such studies only in animals; spatial/area repellents will be used by

humans and the studies are low risk. Humans should be involved in testing earlier rather than later, given appropriate basic scientific data to justify use of human subjects.

Regarding controlled indoor studies versus variable outdoor studies, the purpose for performing the studies (labeling purposes) should be kept in mind. The Board will need to consider the types of statements that can be justified using the results from testing in controlled environments. Because the results will be used to create labels meant to inform consumers, a reference point is needed—it is not sufficient to state that Product A is stronger than Product B. In addition, results obtained under unrealistic conditions cannot be used to state that a specific degree of protection will occur in a real-life situation. The Board must consider how the products will be used by the consumer.

Sample Size and Statistics

Dr. Carriquiry agreed that the objective of the study, including how it will be used to inform EPA labeling practices, must be clearly stated because this will inform study design. Response variables, such as human or non-human subjects, first approach, first bite, or a median lethal dose (LD_{50}) measure need to be clearly defined and justified. Sample size calculations will depend on response variables, the size of effect the investigators wish to detect, and the uncertainty associated with the estimated effect size. Examples for calculating sample size under different conditions exist and should be considered by investigators. The investigators also must understand sources of variability in the experiment, such as the product, environment, or human subjects. Statisticians also should be consulted to ensure that an effective study design is developed. Fractional factorial design might call for 4 fractions at 2 levels (16 different fractions) but studies that require only half this number of levels can be designed. By carefully designing the experiment, investigators may be able to develop designs that more effectively support label claims for protection for more specific circumstances, such as for a certain number of hours under specific wind conditions. She noted that extrapolating from controlled to real-life conditions can be very difficult and may not be necessary if the study is properly designed.

Dr. Johnson reminded the Board that sample size in these experiments refers to replicates of the testing area, whether it is a cage or a real-life setting, such as a patio. Variations in the number of subjects inside the test area will not affect study results. Better data will be obtained if the number of areas in which testing occurs is increased.

Dr. Fish commented that investigators should include justification for the use of humans and for any other experimental choices in protocols and guidelines. Various statements have been made concerning variability in human attractiveness for insects related to age, gender, and race; these differences will affect study design. Dr. Lebowitz added that EPA statements concerning exposure (e.g., brief periods of consistent exposure versus exposure to continuous release) need to be clarified. Mr. Carley clarified that use of continuous versus intermittent exposure will depend on the test. Subject exposure will begin shortly after placement of the emitter, after which exposure will be continuous.

Human Subjects

Dr. Gary Chadwick began by stating that justification for the use of humans in a spatial/area repellent study is required for all protocols. Information on possible non-human studies and how these results will be compared and used together with data from the human studies also should be provided. Justification for the use of humans should address any possible alternative methods. Investigators also should consider human behavior during a test; the effectiveness of a spatial/area repellent may be different when people are sitting still versus moving around and perhaps exiting and re-entering the area covered by the repellent. EPA has stated that humans used as bait in such studies will wear full coverage protective clothing. If such protective clothing is used, the HSRB should be provided with a description or picture of the clothing and information on how it is worn.

Risks and exclusion criteria will vary depending on the type of study, chemical used, and method of dispersal. Regarding the methodological rationale for continuous versus intermittent exposure, again, investigators must consider "real world" behavior such as moving in and out of the area in which the repellent is released. The effect of such behaviors on repellent effectiveness could have implications for labeling. The manner in which the repellent agent is released and the mechanism by which it repels insects (e.g., through irritation or blocking the insects' ability to detect humans) will likely inform exclusion criteria.

EPA should consider whether it requires both laboratory (or cage) tests and field tests; if products are to be compared, laboratory tests would be appropriate, but generating data for label claims might call for field testing.

Dr. Prentice agreed with Dr. Chadwick's conclusions. He commended Dr. Strickman on his explanation of reasons why human subjects may be needed for these tests, e.g., to test repellents that disrupt insect behavior with respect to humans. He emphasized that there must be significant justification for using humans in this research and investigators also must thoroughly explain how they have minimized risks. Drs. Fish and Philpott agreed with Drs. Chadwick and Prentice.

Dr. Fisher commented that the goal of this discussion was to educate Board members and also provide guidance to EPA and sponsors who may be submitting such protocols about the questions the Board may have and the justifications that are expected. She advised Board members to keep in mind that they will be setting standards for required experimental justifications as they write their summaries of the discussions. She summarized several main points made by the Board.

- The need for human subjects must be justified. This justification should include description of any preceding laboratory studies, whether or not animal studies would suffice, risk mitigation procedures, and whether human testing actually would result in less information about repellent properties than if humans were not used.
- Study design and objective, which includes the analyses used in making labeling decisions, are highly important. The Board wishes to emphasize this point and its

importance to the Board's ability to evaluate whether the studies are sufficient for EPA's goals for use of the data.

- Empirical evidence for environmental and gender differences and the effects of area size on repellent effectiveness is needed.
- Information on ambient concentration and how it is determined should be provided.
- Investigators should justify use of field or controlled laboratory conditions, which will require clear statements regarding why testing is being performed and whether the data will be used to determine relative protection or other measures of effectiveness.
- The extent to which protective garments interfere with accurate assessment of repellent efficacy.

At the next HSRB meeting, the Board will discuss issues raised during this teleconference, particularly how charge questions should be defined to allow the Board to clearly address potential protocol deviations, statistical analyses, and generalizability of data. The Board also will address how previously published data should be used to judge the validity of a proposed study, and the usefulness of EPA labeling information for Board decisions. Dr. Fisher will meet with Drs. Whung, Lux and Lewis (OSA, EPA) in March 2009 to organize this session at a future HSRB meeting. Prior to this EPA meeting, small working groups will be formed to help develop discussion topics.

Concluding Remarks

Mr. Jordan described the agenda for the March-April 2009 HSRB meeting. A Carroll-Loye Biological Research protocol testing field efficacy of two picaridin formulations against black flies will be reviewed. This protocol will be similar to protocols testing efficacy against mosquitoes. The AHETF will present scenario design documents and protocols for analyzing exposure for workers involved in mixing and loading pesticide products in water soluble packets. Testing will be conducted at five locations around the United States. Because mixing and loading is being assessed, rather than pesticide application, recruiting practices will differ from those the Board has previously reviewed. An ICR, Inc. protocol for a field study testing the efficacy of a spatial insect repellent against mosquitoes also will be evaluated. The protocol is now under review at EPA, and the discussions that took place during this call will be considered as the review moves forward.

Dr. Lewis thanked Board members and the public for their participation in the teleconference. He also thanked Dr. Strickman for serving as a consultant and providing insight on spatial/area repellents. The next HSRB meeting is scheduled for the week of March 31, 2009. Dr. Lewis is working with OPP and OSA to finalize the agenda. Because the Board has agreed to release an initial draft of their report 2 weeks before the next Board meeting, Dr. Lewis asked lead discussants to complete drafts of their section of the Board report for today's teleconference by February 27, 2009.

Dr. Brimijoin informed Board members that this was his last official HSRB meeting. He thanked his colleagues for providing an enjoyable and stimulating experience and thanked EPA

for inviting him to participate in the HSRB process. The Chair and Board members thanked Dr. Brimijoin for his contributions and indicated he would be missed.

The meeting was adjourned by the Chair.

Respectfully submitted:

Paul I. Lewis, Ph.D.
Designated Federal Officer
Human Studies Review Board
United States Environmental Protection Agency

Certified to be true by:

Celia B. Fisher, Ph.D.
Chair
Human Studies Review Board
United States Environmental Protection Agency

NOTE AND DISCLAIMER: The minutes of this public meeting reflect diverse ideas and suggestions offered by Board members during the course of deliberations within the meeting. Such ideas, suggestions, and deliberations do not necessarily reflect definitive consensus advice from the Board members. The reader is cautioned to not rely on the minutes to represent final, approved, consensus advice and recommendations offered to the Agency. Such advice and recommendations may be found in the final report prepared and transmitted to the EPA Science Advisor following the public meeting.

Attachments

Attachment A	HSRB Members
Attachment B	Federal Register Notice Announcing Meeting
Attachment C	Meeting Agenda

Attachment A

EPA HUMAN STUDIES REVIEW BOARD MEMBERS

Chair

Celia B. Fisher, Ph.D.
Marie Ward Doty Professor of Psychology
Director, Center for Ethics Education
Fordham University
Bronx, NY

Vice Chair

William S. Brimijoin, Ph.D.
Chair and Professor
Molecular Pharmacology and Experimental Therapeutics
Mayo Foundation
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Members

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Department of Statistics
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Ames, IA

Gary L. Chadwick, PharmD, MPH, CIP
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Director, Office for Human Subjects Protection
University of Rochester
Rochester, NY

Janice Chambers, Ph.D., D.A.B.T.
William L. Giles Distinguished Professor
Director, Center for Environmental Health Sciences
College of Veterinary Medicine
Mississippi State University
Mississippi State, MS

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Sean Philpott, Ph.D., M.Bioethics
Science and Ethics Officer
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Professor of Genetics, Cell Biology and Anatomy
Professor of Preventive and Societal Medicine
University of Nebraska Medical Center
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Linda J. Young, Ph.D.
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Gainesville, FL

Consultant to the Board

Daniel Strickman, Ph.D.
National Program Leader
Veterinary, Medical, and Urban Entomology
USDA Agricultural Research Service
Beltsville, MD

* Not in attendance at the February 17, 2008 teleconference

Attachment B

Federal Register Notice Announcing Meeting

Human Studies Review Board (HSRB); Notification of Public Teleconference Meeting

[Federal Register: January 30, 2009 (Volume 74, Number 19)]
[Notices]
[Page 5653-5655]
From the Federal Register Online via GPO Access [wais.access.gpo.gov]

ENVIRONMENTAL PROTECTION AGENCY
[EPA-HQ-ORD-2009-0030; FRL-8769-9]

Human Studies Review Board (HSRB); Notice of a Public Teleconference Meeting

AGENCY: Environmental Protection Agency (EPA).
ACTION: Notice.

SUMMARY: The U.S. Environmental Protection Agency's (EPA or Agency) Office of the Science Advisor (OSA) announces a public meeting of the Human Studies Review Board (HSRB) to advise the Agency on EPA's scientific and ethical review of human subjects research. The HSRB will hold a Public teleconference to discuss two completed field studies by Carroll-Loye Biological Research of mosquito repellent efficacy, and spatial insect repellent technology.

DATES: The teleconference will be held on February 17, 2009, from 11:30 to approximately 4 p.m. (Eastern Time).

Location: The meeting will take place via telephone only.

Meeting Access: For information on access or services for individuals with disabilities, please contact Lu-Ann Kleibacker prior to the meeting using the information under **FOR FURTHER INFORMATION CONTACT**, so that appropriate arrangements can be made.

Procedures for Providing Public Input: Interested members of the public may submit relevant written or oral comments for the HSRB to consider during the advisory process. Additional information concerning submission of relevant written or oral comments is provided in section D. of this notice.

FOR FURTHER INFORMATION CONTACT: Members of the public who wish to obtain the call-in number and access code to participate in the telephone conference, or who wish further information may contact Lu-Ann Kleibacker, EPA, Office of the Science Advisor (8105), Environmental Protection Agency, 1200 Pennsylvania Avenue, NW., Washington, DC 20460; or via telephone/voice mail at (202) 564–7189 or via e-mail at *kleibacker.lu-ann@epa.gov.* General information concerning the EPA HSRB is on the EPA Web site at *http://www.epa.gov/osa/ hsrb/.*

ADDRESSES: Submit your written comments, identified by Docket ID No. EPA–HQ–ORD–2009–0030, by one of the following methods:

http://www.regulations.gov: Follow the on-line instructions for submitting comments.

E-mail: ORD.Docket@epa.gov.

Mail: ORD Docket, Environmental Protection Agency, Mailcode: 28221T, 1200 Pennsylvania Ave., NW., Washington, DC 20460.

Hand Delivery: EPA Docket Center (EPA/DC), Public Reading Room, Infoterra Room (Room Number 3334), EPA West Building, 1301 Constitution Avenue, NW., Washington, DC 20460, Attention Docket ID No. EPA–ORD–2009–0030. Deliveries are only accepted from 8:30 a.m. to 4:30 p.m., Monday through Friday, excluding legal holidays. Special arrangements should be made for deliveries of boxed information.

Instructions: Direct your comments to Docket ID No. EPA–HQ–ORD–2009– 0030. EPA's policy is that all comments received will be included in the public docket without change and may be made available online at *http://www.regulations.gov,* including any personal information provided, unless the comment includes information claimed to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Do not submit information that you consider to be CBI or otherwise protected through *http:// www.regulations.gov* or e-mail. The *http://www.regulations.gov* Web site is an "anonymous access" system, which means EPA will not know your identity or contact information unless you provide it in the body of your comment. If you send an e-mail comment directly to EPA, without going through *http://www.regulations.gov,* your e-mail address will be automatically captured and included as part of the comment that is placed in the public docket and made available on the Internet. If you submit an electronic comment, EPA recommends that you include your name and other contact information in the body of your comment and with any disk or CD–ROM you submit. If EPA cannot read your comment due to technical difficulties and cannot contact you for clarification, EPA may not be able to consider your comment. Electronic files should avoid the use of special characters, any form of encryption, and be free of any defects or viruses.

A. Does This Action Apply to Me?

This action is directed to the public in general. This action may, however, be of interest to persons who conduct or assess human studies on substances regulated by EPA or to persons who are or may be required to conduct testing of chemical substances under the Federal Food, Drug, and Cosmetic Act (FFDCA) or the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). Since other entities may also be interested, the Agency has not attempted to describe all the specific entities that may be affected by this action. If you have any questions regarding the applicability of this action to a particular entity, consult the person listed under **FOR FURTHER INFORMATION CONTACT**.

B. How Can I Access Electronic Copies of This Document and Other Related Information?

In addition to using regulations.gov, you may access this **Federal Register** document electronically through the EPA Internet under the **Federal Register** listings at *http://www.epa.gov/fedrgstr/.*

Docket: All documents in the docket are listed in the index under the docket number. Even though it will be listed by title in the index, some information is not publicly available, e.g., CBI or other information whose disclosure is restricted by statute. Copyright material, will be publicly available only in hard copy. Publicly available docket materials are available either electronically in *http://www.regulations.gov* or in hard copy at the ORD Docket, EPA/DC, Public Reading Room, Infoterra Room (Room Number 3334), 1301 Constitution Ave., NW., Washington, DC. The Public Reading Room is open from 8:30 a.m. to 4:30 p.m., Monday through Friday, excluding legal holidays. The telephone number for the Public Reading Room is (202) 566–1744, and the telephone number for the ORD Docket is (202) 566–1752.

C. What Should I Consider as I Prepare My Comments for EPA?

You may find the following suggestions helpful for preparing your comments:

1. Explain your views as clearly as possible.

2. Describe any assumptions that you used.
3. Provide copies of any technical information and/or data you use that support your views.
4. Provide specific examples to illustrate your concerns and suggest alternatives.
5. To ensure proper receipt by EPA, be sure to identify the docket ID number assigned to this action in the subject line on the first page of your response. You may also provide the name, date and **Federal Register** citation.

D. How May I Participate in This Meeting?

You may participate in this meeting by following the instructions in this section. For information on access to the teleconference, please contact Lu-Ann Kleibacker prior to the meeting using the information under **FOR FURTHER INFORMATION CONTACT**.

1. Oral Comments

Requests to present oral comments will be accepted up to February 9, 2009. To the extent that time permits, interested persons who have not pre-registered may be permitted by the Chair of the HSRB to present oral comments at the meeting. Each individual or group wishing to make brief oral comments to the HSRB is strongly advised to submit their request (preferably via e-mail) to Lu-Ann Kleibacker listed under **FOR FURTHER INFORMATION CONTACT** in order to be included on the meeting agenda and to provide sufficient time for the HSRB Chair and HSRB DFO to review the meeting agenda to provide an appropriate public comment period. The request should identify the name of the individual making the presentation and the organization (if any) the individual will represent. Oral comments before the HSRB are limited to 5 minutes per individual or organization. Please note that this includes all individuals appearing either as part of, or on behalf of an organization. While it is our intent to hear a full range of oral comments on the science and ethics issues under discussion, it is not our intent to permit organizations to expand the time limitations by having numerous individuals sign up separately to speak on their behalf. If additional time is available, there may be flexibility in time for public comments.

2. Written Comments

Although you may submit written comments at any time, for the HSRB to have the best opportunity to review and consider your comments as it deliberates on its report, you should submit your comments at least five business days prior to the beginning of the meeting. If you submit comments after this date, those comments will be provided to the Board members, but you should recognize that the Board members may not have adequate time to consider those comments prior to making a decision. Thus, if you plan to submit written comments, the Agency strongly encourages you to submit such comments no later than noon, EST, February 9, 2009. To ensure proper receipt of all written material by EPA, it is imperative that you identify docket ID number EPA–HQ–ORD–2009–0030 in the subject line on the first page of your submission. In addition, the Agency also requests that person(s) submitting comments directly to the docket also provide a copy of their comments to Lu-Ann Kleibacker listed under **FOR FURTHER INFORMATION CONTACT**. There is no limit on the length of written comments for consideration by the HSRB.

E. Background

1. Human Studies Review Board

The HSRB is a Federal advisory committee operating in accordance with the Federal Advisory Committee Act (FACA) 5 U.S.C. App.2 section 9. The HSRB provides advice, information, and recommendations to EPA on issues related to scientific and ethical aspects of human subjects research. The major objectives of the HSRB are to provide advice and recommendations on: a. Research proposals and protocols; b. reports of completed research with human subjects; and c. how to strengthen EPA's

programs for protection of human subjects of research. The HSRB reports to the EPA Administrator through EPA's Science Advisor.

The EPA will present for HSRB review scientific and ethical issues surrounding the reports from a completed field study of mosquito repellent efficacy (SPC–001) and a completed laboratory study of tick repellent efficacy (SPC–002) conducted by Carroll-Loye Biological Research using multiple skin-applied repellent products containing picaridin. In addition, the HSRB will consider and discuss general information about ''spatial'' or ''area'' insect repellent products and their testing, in preparation for expected future reviews of proposals for field efficacy testing of spatial repellents. Insect repellent testing reviewed by the Board in past meetings has concerned only skin-applied repellents, which differ in important ways from spatial repellents. Finally, the HSRB may also discuss planning for future HSRB meetings.

2. Meeting Minutes and Reports

Minutes of the meeting, summarizing the matters discussed and recommendations made, if any, by the advisory committee regarding such matters will be released within 90 calendar days of the meeting. Such minutes will be available at *http:// www.epa.gov/osa/hsrb/* and *http:// www.regulations.gov.* In addition, information concerning a Board meeting report, if applicable, can be found at *http://www.epa.gov/osa/hsrb/* or from the person listed under **FOR FURTHER INFORMATION CONTACT**.

Dated: January 26, 2009.
Kevin Teichman,
EPA Acting Science Advisor.
[FR Doc. E9–2037 Filed 1–29–09; 8:45 am]
BILLING CODE 6560–50–P

Attachment C

2/12/2009

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
HUMAN STUDIES REVIEW BOARD (HSRB)
FEBRUARY 17, 2009
PUBLIC TELECONFERENCE MEETING

HSRB WEB SITE http://www.epa.gov/osa/hsrb/
Docket Telephone: (202) 566 1752
Docket Number: EPA–HQ–ORD–2009–0030

Meeting by Teleconference
Call 202 564 7189 for the teleconference number

- **12:30 PM** **Convene Meeting and Identification of Board Members** – Celia Fisher, Ph.D. (HSRB Chair)
- **12:40 PM** **Meeting Administrative Procedures** – Paul Lewis, Ph.D. (Designated Federal Officer [DFO], HSRB, Office of the Science Advisor [OSA], EPA)
- **12:45 PM** **Welcome –** Pai-Yei Whung, Ph.D. (Chief Scientist, OSA, EPA)
- **12:55 PM** **EPA Follow-up on Pesticide Specific HSRB Recommendations –** Mr. William Jordan (Office of Pesticide Programs [OPP], EPA)

Carroll-Loye Biological Research Tick Repellent Efficacy Study (SPC-002)

- **1:05 PM** **Carroll-Loye Biological Research Tick Repellent Efficacy Study (SPC-002) –** Mr. Kevin Sweeney (OPP, EPA) and Mr. John Carley (OPP, EPA)
- **1:25 PM** **Public Comments**
- **1:35 PM** **Board Discussion**

Is study SPC-002 sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy against ticks of the three formulations tested?

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

Carroll-Loye Biological Research Mosquito Repellent Efficacy Study (SPC-001)

- **1:55 PM** **EPA Science and Ethics Assessment of Carroll-Loye Biological Research Mosquito Repellent Efficacy Study (SPC-001) –** Mr. Kevin Sweeney (OPP, EPA) and Mr. John Carley (OPP, EPA)
- **2:15 PM** **Public Comments**
- **2:25 PM** **Board Discussion**

Is study SPC-001 sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy against mosquitoes of the three formulations tested?

Does available information support a determination that study SPC-001 was conducted in substantial compliance with subparts K and L 40 CFR Part 26?

• **2:45 PM Break**

Spatial/area Insect Repellent Testing

• **2:50 PM Introduction –** Celia Fisher, Ph.D. (HSRB Chair)
• **2:55 PM Technical Aspects of Spatial/Area Repellent Testing –** HSRB Consultant
• **3:15 PM Board Discussion**

Environmental Aspects

1. What are the environmental (temperature, wind, time of day, humidity, proximity to water/plants, size and type of space) and human factors (height/weight; gender, age, ethnicity, density of humans in space) that can affect insect behavior and repellent efficacy relevant to space treatment studies?

2. What factors need to be considered for test spaces with respect to size of area in which the test is conducted? How is the most appropriate test area determined?

3. Does the number of human subjects within testing environments of different sizes affect insect activity? Does the number of subjects in a given area affect product efficacy or the measurement of product efficacy?

4. Are there any other special considerations regarding insect behavior in such studies that require inclusion in protocols?

Study Design

1. How is the location of open spaces typically selected? How many different or similar types of sites are appropriate to assess generalizability?

2. What are common spatial dispensing devices? How are they related to the nature of the product dispensed (e.g., gas, suspended liquid, smoke)? What are design or measurement challenges for different dispensing devices and products?

3. What type of dosimetry data is required to determine amount of product application used in testing? How is discharge time determined? What are the relative design merits of the experimenter or subject discharging the repellent?

4. How are outcomes measured in these studies? How are insect knockdown and mortality effects measured? Are both knockdown and landings/bites usually measured in the same study? What is the difference in knockdowns vs bites in terms of information regarding product efficacy/effectiveness?

5. What is the difference with respect to measurement in assessing efficacy of the active ingredient and effectiveness of the formulation?

Sample Size and Statistics

1. Depending on the outcome measure, what are best practices with respect to human sample size? What is the sample size norm in the field? How is determination of sample size related to square feet of test area? What is the best way to determine power for these studies?

2. What are best practices with respect to statistical analysis? How is censored data handled?

3. What are the pros and cons of various endpoints (e.g. ending the study after a set number of hours, waiting until the first landing/bite, other) to assess product efficacy (e.g. to meet assumptions for appropriate statistical analyses)?

Human Subjects

1. Why are human subjects necessary for such studies if the outcome measures are knockdowns or mortality?

2. What are the potential risks to treated subjects (e.g. inhalation, dermal effects)? What are exclusion criteria in subject selection to avoid such risks? How is the degree of risk related to dosage, ingredient, formulations, aerosol pressure?

3. What is the methodological rationale for continuous versus intermittent exposure? How do human risk differ for these types of exposures? Will exposure start at the beginning of the test period immediately after release of the product?

4. If the test agent has properties to repel or destroy an insect, what is the relationship (if any) to a related mechanism of action to humans?

- **4:45 PM** **Concluding Remarks –** Mr. William Jordan (OPP, EPA)
- **4:50 PM** **Adjournment –** Celia Fisher, Ph.D. (HSRB Chair) and Paul Lewis, Ph.D. (HSRB DFO)

* Please be advised that agenda times are approximate and subject to change. For further information including the teleconference phone number please contact Lu-Ann Kleibacker via telephone at 202 564 7189 or email: kleibacker.lu-ann@epa.gov