2/16/07

Minutes of the
United States Environmental Protection Agency (EPA)
Human Studies Review Board (HSRB)
January 24, 2007 Public Meeting
Docket Number: EPA-HQ-ORD-2006-0998
HSRB Web Site: http://www.epa.gov/osa/hsrb/

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

Dates and Times:	Wednesday, January 24, 2007, 8:30 AM – 4:30 PM (See Federal Register Notice – Attachment B)	
Location:	Sheraton Crystal City Hotel, 1800 Jefferson Davis Highway, Arlington, VA 22202	
Purpose:	The EPA Human Studies Review Board (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.
	Board Members:	David C. Bellinger, Ph.D. Alicia Carriquiry, Ph.D. Gary L. Chadwick, PharmD, MPH, CIP Janice Chambers, Ph.D., D.A.B.T. Susan S. Fish, PharmD, MPH Suzanne C. Fitzpatrick, Ph.D., D.A.B.T. KyungMann Kim, Ph.D., CCRP Kannan Krishnan, Ph.D. Michael D. Lebowitz, Ph.D., FCCP Sean M. Philpott, Ph.D. Richard Sharp, 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 (HSRB Chair) welcomed Board members, U.S. Environmental Protection Agency (EPA or Agency) staff, and members of the public to the first HSRB meeting of 2007. She thanked Board members for their participation and called for introductions. Dr. Fisher acknowledged Dr. Paul Lewis (Designated Federal Officer [DFO], HSRB, Office of the Science Advisor [OSA], EPA) for his assistance with and contributions to Board activities.

She informed Board members of planning meetings she had with EPA officials and commended the Agency's helpfulness and responsiveness to issues raised during previous Board meetings.

Welcoming Remarks

Dr. George Gray (EPA Science Advisor) thanked the HSRB for its efforts in this review process. He introduced Mr. Jim Jones (Director, Office of Pesticide Programs [OPP], EPA). He expressed appreciation for Board efforts on its previous reports, which have been useful for EPA as EPA considers its approach to regulatory decisions and for decision making regarding research performed and funded by EPA. He commented that this meeting represents the first meeting at which the entire review process—submission of a protocol, identification of Board concerns, response to those concerns and adjustment of the protocol by study sponsors, presentation of study results and Board review has been completed. EPA appreciates the timeliness of the Board's efforts. Today provides an opportunity for Board members to see the impact their work has had on the process.

Dr. Gray thanked his EPA colleagues for their work in support of the HSRB. He welcomed public comments at today's meeting. The HSRB is an open and transparent board and the advice of the HSRB helps EPA make sound decisions based on strong science. Dr. Gray concluded that he looks forward to future open and thoughtful analysis and advice from the HSRB.

Opening Remarks

Mr. Jones re-iterated the value of the HSRB's work to EPA staff. He informed Board members that EPA has found the new approval process for pesticide studies involving humans to be effective and result in excellent advice useful for decision making. He indicated that results would be presented from studies on tick and mosquito repellent products that have undergone the entire Agency and HSRB review process, including assessment of both scientific and ethical issues. HSRB advice has been invaluable for informing EPA of ways to perform these studies while assuring protection of the participants, which is of significant importance to EPA's function as a regulatory agency.

Meeting Administrative Procedures

Dr. Lewis welcomed Board members and thanked them for their work. He welcomed members of the public and his EPA colleagues. As DFO, Dr. Lewis serves as liaison between the HSRB and EPA and ensures that Federal Advisory Committee Act (FACA) requirements - open meetings, timely meeting announcements in the *Federal Register*, and meeting materials are made available at a public docket. 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 Office of the Science Advisor Deputy Ethics Officer in consultation with EPA's Office of General Counsel (OGC) to ensure that all ethics disclosure requirements have been met. Dr. Lewis reminded participants that meeting times would be approximate and that public comments would be limited to five minutes.

Meeting Process

Dr. Fisher reviewed the process for meeting operations, HSRB responsibilities, the HSRB Charter, Board process, and major objectives. She stated that the Board seeks to clarify and develop criteria to evaluate the science and ethics of different types of completed research and protocols, allowing for fairness and consistency. She commented that initial review of protocols is not *a priori* approval of studies already performed; the Board examines completed studies as carefully as proposed studies. The Board takes seriously its responsibility to review protocols and determine the sponsors' responsiveness to issues raised during the initial review, as well as the caliber of the data.

The HSRB review begins with a presentation by EPA of the scientific and ethical considerations on the studies under review. This presentation is followed by clarifying questions from the HSRB and then public comments on the issues being discussed. Dr. Fisher explained that particular Board members are assigned to be primary reviewers of the studies; their reviews are presented and then deliberated upon by the entire Board.

Scientific considerations would precede ethical considerations because to be ethical, a study must be scientifically valid. Dr. Fisher stated that the Board would assess both the scientific and ethical validity of a protocol, including procedures, dose selection, endpoint selection, social value of the research, appropriateness of control and experimental groups, methods including statistical analyses, and selection of target populations and derivation of sample sizes. The Board would review how well established protocols were followed and also examine the handling of unexpected events from both a scientific and ethical perspective.

Dr. Fisher commended EPA's effort in fitting protocols to HSRB guidelines and in informing sponsors of HSRB and EPA information needs in order to conduct a thorough review. She also commended efforts to justify the use of human subjects and thoroughly document potential risks.

Update on EPA Follow-up of HSRB Recommendations

Mr. William Jordan (OPP, EPA) introduced Mr. John Carley (OPP, EPA), lead for the ethical review; Dr. Clara Fuentes (OPP, EPA), lead for the scientific review; and Dr. Warren Lux, (Human Subjects Research Review Official [HSRRO], OSA, EPA). Dr. Lux ensured that EPA's efforts are compatible, consistent, and compliant with its responsibility to protect subjects of human research.

Mr. Jordan reported how EPA used the Board's recommendations concerning studies reviewed at meetings held in the summer and fall of 2006:

(1) The HSRB reviewed the Chromium Repeat Open Application Test (ROAT) study with Acid Copper Chromate (ACC), which provided EPA with useful scientific information for risk assessment activities and assurance that the study met acceptable ethical standards. The Board recommended that EPA combine both irritant and

sensitization reactions to determine the 10 percent (%) minimum elicitation threshold value (MET_{10}) for this substance and recommended against a proposed normalization protocol of test subjects to subjects in the North American Contact Dermatitis Group (NACDG). EPA used these recommendations and the results of the study to develop a risk assessment for dermal exposure of workers and the general public who could come into contact with ACC-treated wood used in residential construction. EPA concluded that the potential for sensitization and irritation associated with contact with ACC-treated wood was sufficient to warrant EPA regulatory action to deny an application for residential use of ACC-treated wood.

(2) Insect Repellent Efficacy Protocols EMD-003 and EMD-004 were originally assessed in June 2006. The lead investigator on these protocols, Dr. Scott Carroll (Carroll-Loye Biological Research, Inc.), revised the protocols based on Board advice and the protocols were again reviewed by the Board at its October 2006 meeting. The Board deemed the protocols to be scientifically sound, likely to produce reliable data, and to meet ethical standards. Mr. Jordan stated that Dr. Carroll has since completed the research and submitted the results to EPA. He reported that EPA had reviewed the research and would present the reviews to the Board during this meeting.

(3) The Board reviewed draft EPA guidance to submitters of protocols for proposed new human research and suggested several changes. Mr. Jordan stated that EPA plans to revise the draft guidance in the coming months, incorporating the HSRB's suggestions, and seek to engage stakeholders by soliciting general public comment on the draft. He explained that as EPA has gained experience in these processes, the Agency has realized the competing needs to provide sufficient information for review while considering confidential business information (CBI) claims; issues of timing of studies; and problems associated with serial submissions of supporting documents, rather than one complete package.

(4) The HSRB also offered suggestions for how EPA and researchers can submit materials requiring HSRB review when some of the materials are subject to CBI claims. Mr. Jordan indicated that EPA will work with Drs. Fisher and Lewis and the OGC to resolve this issue. EPA also will work with submitters to ensure that materials claimed confidential are protected from unlawful disclosure and will work with the HSRB to promote the greatest degree of transparency in the Board's review of materials allowed under the statute.

(5) The Board previously reviewed several protocols developed by the Agricultural Handlers Exposure Task Force (AHETF) and provided extensive comments on both the study design from a scientific perspective and on ethical issues that arise in the conduct of such studies. EPA analyzed their database used for assessing exposure of pesticide handlers and presented their analysis at the January 2007 meeting of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP). Dr. Janice Chambers participated in this meeting and provided advice on scientific issues. Discussion at the SAP meeting focused on the benefits of obtaining new data on handler exposures; the reliability of passive dosimetry versus

biomonitoring; and various methodological issues, including the proportionality of exposure to the active ingredient, hand rinse efficiency, sample size, and cluster selection, among others. Mr. Jordan commented that the process of preparing for the meeting and receiving feedback from the SAP was useful, and has allowed EPA to be better prepared to present the AHETF protocols to the HSRB for review later in 2007. Mr. Jordan specifically thanked Dr. Chambers for her suggestions regarding the presentations of research and protocols at the SAP meeting.

Mr. Jordan informed Board members that the Board's workload probably would remain heavy and that a number of topics are under consideration for presentation at the April 2007 meeting. EPA will endeavor to use Board resources efficiently.

Dr. Fisher expressed her appreciation for the presentations and commented that the Board received useful feedback on its efforts. She asked Mr. Jordan about a statistical question raised during the Board's June 2006 meeting reviewing the AHETF protocols AHETF meeting concerning a proposed meta-analysis and inquired if SAP had any comments or advice on this issue that might be useful to the Board and study sponsors. Mr. Jordan explained that the SAP addressed three sets of questions related to statistical issues. The first related to establishing sample size, such as how many subjects should be included to develop a robust database that EPA can use for handler exposure assessment. The second concerned whether to take samples repeatedly from the same subject (within-worker variability) or from a larger number of different subjects (between-worker variability). There are advantages to both approaches. The SAP provided useful advice concerning this matter, but EPA will continue to consider both approaches and will develop a concrete proposal and justification with regard to the number of subjects and advantages and disadvantages of each approach. The third issue concerned cluster selection. The AHETF presented essentially identical application protocols performed in different parts of the country at different times of the year. Although the protocols are essentially identical, performing the experiments at different times and places could be a source of variability. The SAP provided information concerning how to select sampling sites to be representative of the exposed worker population. This information will influence the design of the studies. The SAP meeting covered agricultural handler scenarios but also raised questions about the design of exposure studies for those handling antimicrobial disinfectants. The use patterns of agricultural and antimicrobial substances are different, but similar statistical issues apply.

Dr. Fisher thanked Mr. Jordan for informing the Board of the review process procedures and commended EPA on its efforts to seek and effectively use the advice they receive. She recommended that independent consultants or reviewers external from agricultural groups be included in the review process. Mr. Jordan clarified that EPA's presentation to SAP was part of a larger group that included the California Department of Pesticide Regulation, scientists responsible for assuring pesticide safety, and scientists from the Canadian Pesticide Regulatory Authority. This approach allows EPA to draw on resources unique to each organization. EPA has worked with Canada's Pesticide Management Regulatory Agency, which has access to useful scientific expertise. EPA pushes the boundaries to obtain current data to address scientific issues and for regulatory assessment; the same applies for ethics assessments.

Dr. Fisher expressed appreciation for EPA's efforts to address issues raised by the Board. She commented that Board members wish to develop criteria for addressing scientific and ethical issues before their meeting with the AHETF in October 2007. HSRB members wish to discuss criteria prior to receiving protocols, so that sponsors will know how their protocols will be reviewed. She asked whether the HSRB would receive the recommendations developed by SAP to use to develop their own criteria. Mr. Jordan informed Dr. Fisher that minutes from the SAP meeting would be available in late March 2007. He will deliver a copy to the HSRB DFO for subsequent delivery to the Board as soon as possible and will consider Dr. Fisher's request to discuss criteria for these reviews at the April 2007 HSRB meeting. Mr. Jordan added that he believes the AHETF hopes to have its protocols reviewed in October 2007. The Antimicrobial Exposure Task Force (AETF) does not yet have a review schedule and does not have to consider the growing season. The Board might wish, however, to review AEATF protocols in June 2007. Dr. Fisher thanked EPA for its efforts and added that she was impressed with the level of detail in the EPA reviews.

Insect Repellent Completed Efficacy Studies EMD-003 and EMD-004

Introduction

Mr. John Carley provided background and context for insect repellent efficacy studies EMD-003 and EMD-004. Protocol EMD-003 proposed testing 3 formulations of repellent (lotion, pump spray, and aerosol) containing the active ingredient IR-3535 for efficacy in repelling ticks under laboratory conditions. Protocol EMD-004 tested the same 3 formulations for efficacy in repelling mosquitoes under field conditions in two habitats (dense forest and moist pasture or marshland). Guidelines recommended testing in two habitats to assess efficacy in the presence of different mosquito species with different behaviors. Both protocols had a dosimetry phase to establish a "typical consumer dose" that would be used in the efficacy phases of the trials. The same 12 subjects participated in dosimetry testing of the 3 formulations for both protocols. An error in formulation of the aerosol test material caused a delay in testing this formulation, and the reports considered during this meeting addressed testing of only the lotion and pump spray formulations. Separate reports for each formulation (lotion and pump spray) were submitted for each protocol, and then a subsequent report including both formulations was re-submitted.

Since the protocols are third-party research involving intentional exposure of human subjects, intended for submission to EPA under the pesticide laws, and initiated after April 7, 2006, pre-review of the protocol and supporting materials by EPA and the HSRB was required, as was substantial compliance with 40 Code of Federal Regulations (CFR) 26 Subparts K and L. These protocols were among the first considered by the HSRB (in June 2006), were the first protocols reviewed favorably by the HSRB (October 2006), and are the first completed studies as presented here to the HSRB.

Mr. Carley described the series of review cycles the protocols underwent. Review Cycle 1 took from April 18 to October 6, 2006; it began with Independent Investigational Review Board (IIRB) approval of the protocols and submission of the protocols for EPA and HSRB review and discussion. It concluded with delivery of a final report by the HSRB on

October 6, 2006. Review Cycle 2 began with submission of the first revision of the protocols to EPA on July 12, 2006, followed by IIRB approval of the revised protocols, submission of second and third revisions and subsequent IIRB approval, EPA review, and concluded with the HSRB draft HSRB meeting report on December 8, 2006. Review Cycle 3 began with data collection between October 23 and November 1, 2006, followed by report submission to EPA on November 9, 2006, EPA science and ethics reviews, submission of supplemental materials, and concluded at the January 24, 2007 meeting with the HSRB discussion of EPA reviews. The research itself, including the dosimetry phase, mosquito repellent efficacy phase (laboratory and field studies) took place between October 23 and November 1, 2006. The study reports were submitted to EPA on November 9, 2006. Mr. Carley noted that the efficacy phase for the aerosol study was conducted on November 18 and 19, 2006; although these reports had been received by EPA, they would not be discussed during this meeting.

Scientific Considerations

Dr. Fuentes presented the science assessment of protocols EMD-003 and EMD-004. The purpose of the science assessment was to evaluate the validity of the revised protocols, assess their consistency with recommendations made by EPA and the HSRB, and to provide a scientific review of the reported studies. Both protocols were revised consistent with the recommendations, except for minor exceptions. The studies both produced sound data meeting the studies' objective to estimate typical consumer doses and quantify the duration of repellency of the formulations tested against ticks and mosquitoes.

The deviations from the recommended protocols were minor. During the dosimetry phase, the number of practice applications was dropped from 3 to 1, because 3 practice applications were deemed unnecessary. This did not affect the grand mean of the dosimetry phase, because subjects nonetheless performed 3 applications of product. Entry errors were not properly handled in all cases, primarily because data were collected by the subjects themselves, with assistance from a trained technician during the collection process. The errors in the entries were not significant and did not compromise the validity of the results. The dosimeters were not backed with impermeable layers because the dosimeters themselves were sufficiently impermeable. The temperature of the laboratory rose 1^{o}C above expected (to 26^{o}C) for two testing periods, but this did not affect the results. During the dosimetry phase of the protocol, a proposed Friedman 2-way analysis of variance (ANOVA) for comparison between formulations and for assessing possible interaction of formulations with subjects' application differences was omitted, but this analysis was not essential for estimating the typical consumer dose for use in the efficacy evaluation. Similar deviations occurred during the efficacy phase and also did not affect the results. Testing of the aerosol formulation was not included in the protocols at this time.

During the performance phase of EMD-004, product performance was underestimated, which likely contributed to subjects (three treated with pump spray, two treated with lotion) terminating exposure before efficacy failure. The early departure times of these subjects were treated as equivalent to a failure of repellency, leading to a conservative estimate of complete protection time (CPT). Subjects also did not always cover treated limbs between exposures, but

because they stepped out of the test site or entered a screened enclosure, no exposure of treated limbs to mosquitoes occurred between one-minute exposure periods.

Determination of grand means from the dosimetry phase for the lotion formulation gave values of 0.001158 grams per square centimeter (g/cm^2) for arms and 0.001108 g/cm^2 for legs. These numbers represent the arithmetic means of the subject means presented in the report. The text of the report lists these values as 0.0115 g/cm^2 and 0.001114 g/cm^2 for arms and legs, respectively. There was no explanation for this discrepancy or for why the arms and legs had a single target dose. Dr. Fuentes stated that EPA believed that differences at this level of precision can be attributed to differences in documentation. The target dose for the protocol testing the tick repellency of the lotion formulation, EMD-003.1, was 0.00115 milliliters per square centimeter (ml/cm^2) for both arms and legs; this was within the range of standard deviation for the grand means of the dose.

Dr. Fuentes noted that the report of the efficacy phase for EMD-003.1 had an error in transcribing the treatment dose from spreadsheets to the table in the report, but recalculation of the data indicated that all 10 test arms received the correct 0.0011 ml/cm^2 dose. The efficacy phase for EMD-004.1, testing mosquito repellency of the lotion formulation had two testing sites, Butte County (woods) and Glenn County (marsh), CA. The protocol was accurately performed and reported for the Butte County site. For the Glenn County site, the table in Appendix 3 contained errors. One arm appeared to receive a higher dose of the lotion, but recalculation showed that this was due to a transcribing error (arm entered instead of leg). One leg was underdosed (0.008 ml/cm^2) and one was overdosed (0.012 ml/cm^2).

The grand means for the dosimetry phase of the pump spray formulation were 0.00067 g/cm^2 for arms and 0.00051 g/cm^2 for legs. The target doses for the efficacy phase of this formulation were 0.00071 ml/cm^2 (arms) and 0.00054 ml/cm^2 (legs). The difference between the grand means and the target dose were within the standard deviations range. The actual dosing for testing tick and mosquito repellent efficacy for pump spray formulations were correctly calculated and within the standard deviations of the target dose.

The results of the efficacy phase for tick repellency indicated a mean CPT of 9.1 hours ± 2.5 hours for the lotion (EMD-003.1), with a range of 5 to 12 hours, and a mean CPT of 12.1 hours ± 2.8 hours with a range of 6.5 to 15 hours for the pump spray formulation (EMD-003.2). The results of the efficacy phase for mosquito repellency for the lotion formulation (EMD-004.1) indicated a mean CPT of 7.3 hours ± 0.93 hours at the forest site and 8.5 hours ± 0.84 hours for the marsh pasture site. The results of the pump spray formulation (EMD-004.2) were mean CPTs of 7.1 hours ± 0.99 hours for the forest site and 8.4 hours ± 0.84 hours for the marsh/pasture site.

EPA concluded that the dosimetry phase of the study to determine typical consumer dose is a strength of the revised protocol and the repellency studies. The minor deviations from the protocols did not compromise the validity of the data or the results of the tests, and both EMD-003 and EMD-004 study designs produced scientifically reliable data that met the studies' objectives.

Dr. Fisher expressed skepticism that the deviations from the recommended procedures were minor, as stated in the Agency's summary. The study enrolled only 12 subjects, and some over- or under-applied the lotion. Any means or efficacy scores will be evaluated based on this, so it is surprising that the effects of this error were minor.

Dr. Fisher also advised that the language, "guided by or in response to" be used instead of "consistent with" recommendations. "Consistent with" implies that the study was perfectly designed and well-implemented; however, if data analysis of the 12 subjects in the study included subjects who did not apply the repellent properly, the study was not perfectly implemented. She also inquired how, if the same 12 subjects were used repeatedly in this study, the results would apply to the general population, and if this sample size was truly sufficient to be considered representative of consumer application techniques and to support risk assessment activities. Dr. Fisher added that many errors in data collection and analysis occurred, despite the small sample size, and wondered why the onus was on EPA to correct these errors.

Mr. Carley clarified that 12 subjects were used for the dosimetry study and 10 subjects for each formulation for the repellent phase; this did not necessarily include the same 12 subjects. He explained that the historical rule of thumb for dosimetry states that a typical application is 1 gm/600cm^2, which is assumed to be appropriate regardless of the formulation or concentration of the formulation. These studies showed that there are important differences in application that vary with the site of application (leg versus arm) and formulation (spray versus lotion). He commented that each of the 12 subjects in the trial were appropriately representative. Each subject applied the material 3 times, the mean application amount was determined, and the grand mean calculated for the group. Dosage errors occurred only at Site 2 for efficacy testing against mosquitoes; all other errors were errors in reporting. Mr. Carley stated that he did not believe the study was performed carelessly.

Dr. Susan Fish commented that if the grand mean of the means is used as a recommended dose, and this is generalized to the population as a whole, half of the general public will likely apply half the dose tested. She acknowledged that although there may be historical reasons for using this calculation, using the lower quartile to determine recommended dose may more effectively account for people who apply less product. Mr. Carley recommended that the HSRB discuss this issue when reviewing the new protocol (SCI-001) that would be presented in the afternoon. The proposal to perform the dosimetry experiments using the described method was reviewed at the last two HSRB meetings, although the level of variability in the results was unanticipated.

Dr. Alicia Carriquiry inquired about the effect of individuals serving as their own internal control in the tick repellency study. Mr. Carley clarified that in the tick study, the untreated arm is used to confirm that the ticks showed active questing behavior and were appropriate to use for testing the effect of the repellent applied to the subject's other arm. Dr. Carriquiry asked why the CPT was not calculated as the difference between the distances the tick traveled on the treated arms compared to the untreated arms. Mr. Carley explained that the repellency on the untreated arm would be 0.

Dr. Gary Chadwick questioned the relatively high withdrawal rate (20-30%) of subjects before efficacy failure and asked about the reasons for withdrawal, as well as the effects this had on the results. Dr. Fish clarified that because the subjects did not complete the entire 10 hours of testing, their withdrawal times, for example, 8 to 9 hours into the testing session, were considered their CPT; this would underestimate product performance. Dr. Chambers asked how the CPT data would be used to develop labels for the products. Dr. Fisher explained that a minimal time based on the CPT average would be used, if standard deviation is used, the minimal time may be less than the CPT average.

Dr. Kannan Krishnan expressed concern about the toxicity of the products. He commented on the lack of comparison between the dosages received in the dosimetry studies compared to a toxicity benchmark, such as the lowest observed adverse effect level (LOAEL). Dr. Fisher answered that toxicity information for this test material was available before commencement of the study. Mr. Carley explained that most subjects were treated with approximately 1 gram of product. Assuming an average weight of 75 kilograms (kg), most subjects would receive approximately 14 milligrams (mg)/kg. The acute oral toxicity for IR-3535 is more than 5,000 mg/kg, dermal toxicity is more than 2,000 mg/kg. Mr. Carley stated that the materials tested are intended for continuous skin contact, are designed to be innocuous, and have been tested in toxicity studies. He reported that EPA is comfortable with the use of these formulations for continuous skin contact, and the levels used in these studies did not represent a serious toxicity risk. Dr. Krishnan recommended including a statement to this effect in the report.

Dr. KyungMann Kim asked for clarification of the data collection process, particularly concerning the deviation from the protocol stating that each subject collected his or her own data , in contrast to the study report stating that the study director recorded the data. Dr. Fuentes explained that each subject was trained to collect data with the supervision of a trained technician. Dr. Fisher added that although subjects collected data in the field, the report of the data was written by the investigators. Dr. Lebowitz commented that it would be useful for the HSRB to have the evidence used by EPA to determine that the deviations did not affect the study results. Because the number of subjects was small, any deviations could affect both the within-subject means and the between-subject grand means.

Dr. Fisher commented that the variability observed in the dosage study was unanticipated. She asked whether the study gave EPA sufficient information despite the variability and whether another step besides determination of grand means was needed. Dr. Fuentes answered that the purpose of the dosimetry study was to ensure the safety of the subject. If the dosage values were determined to be below the LOAEL, EPA considered the product to be safe.

Dr. Janet Andersen (OPP, EPA) explained how EPA reports efficacy. If a product is determined to work for a given number of hours, EPA uses a conservative analysis of the data to label the product. If CPT is determined to be 9 hours ± 2.5 hours, EPA would label the product as effective for 6 hours. Dr. Andersen indicated that the labels usually include comments cautioning that efficacy can vary based on individual human characteristics (for example, sweating) and would state that the product should be reapplied as often as necessary. She noted that EPA recognizes that this number would not be precise because of the variability among

humans. EPA provides this sort of guidance to help registrants decide how to label their products. Dr. Anderson added that EPA has a Label Review Manual used by regulatory staff for guidance; this manual is publicly available on EPA's Web site. Mr. Carley clarified that the labels provide information for consumers to make informed decisions about which product to use. The label does not provide a prediction of how long a product will work for a given individual, given that different people respond differently to the product and pests are of different species and behave differently in different environments.

Ethical Considerations

Mr. Carley described the EPA's ethics assessment of EMD-003 and EMD-004. The documents considered in this review included the initial submissions received on November 9, 2006, revised submissions received on December 15, 2006, EPA's protocol review dated September 15, 2006, and the HSRB final draft meeting report dated December 8, 2006. Additional information included in the review was an email dated December 19, 2006 from Dr. Carroll concerning dates the study was conducted and use of the September 12, 2006 informed consent form (ICF), and correspondence between Dr. Carroll and the IIRB in September 2006.

Protocols EMD-003 and EMD-004 met the applicable ethical standards 40 CFR §26.1125, 40 CFR §26.1601, 40 CFR §26.1303, 40 CFR §26.1703, and 40 CFR §26.1705. These protocols also met the requirements for completeness of documentation (40 CFR §26.1303). Although all required documents were submitted, no single complete report exists (documents were submitted serially).

Deviations from the protocol did not present ethical problems. Data collection began before IIRB approval of the revised protocol and the ICF. However, data collection was performed under a prior, IIRB-approved protocol (dated September 12, 2006) and thus does not constitute an ethical violation. Data collection preceding quality assurance (QA) review was considered a technical violation without ethical impact. Dropping of the aerosol testing phase was reported only in the transmittal document, but the effect was only to confuse the reader and did not have an ethical effect.

In response to the HSRB recommendations, the investigators designated an on-call physician, clarified potential adverse effects in the ICF (EMD-003 only), and moved ICF discussion of compensation out of the "Benefits" section. These changes were not implemented before subjects were recruited, consented, and tested using the lotion and pump spray formulations.

In summary, there was no evidence that the procedures of the IIRB were violated. Although data collection preceded IIRB approval of final changes to the protocol and ICF, these changes were minor and the protocol and ICF used had been approved by the IIRB in September 2006, and favorably reviewed by the HSRB in October 2006. Some of these irregularities might have resulted from the haste of the process; nonetheless, the research was compliant with ethical standards. All required documentation was provided, and there was no

evidence that the subjects were misled or endangered by the delay in implementing the changes suggested by the HSRB. The study is in compliance with the applicable statutes.

EMD-003 and EMD-004 generated large numbers of documents and large amounts of information. The protocols and reports were more complete in both design and execution than those usually reviewed by EPA and the HSRB. The investigator has worked in good faith to understand and incorporate the new rules implemented by EPA to ensure that research involving humans meets the highest ethical and human standards. Many of the discrepancies observed arose because the record of these studies is so extensive. The main criticisms to these studies include some difficulties in QA that likely arose because of the haste with which the studies were performed and reported.

Public Comment

Dr. Scott Carroll of Carroll-Loye Biological Research, Inc.

Dr. Carroll expressed his appreciation for the input and guidance provided by the HSRB. To address the question of dosimetry errors, Dr. Carroll confirmed that in 2 of 60 applications for efficacy, errors were made in dosing. In one case, 0.0008 ml/cm^2 instead of 0.011 ml/cm^2 was applied, in the other 0.012 ml/cm^2 was applied. The subject dosed at the lower rate had a lower CPT, and the subject who received a higher dose had a longer CPT, although this subject had a mosquito land earlier than other subjects. These errors did not impact the quality of the data.

Because the studies were performed on a tight schedule, Dr. Carroll used previously approved ICFs. He reviewed the compensation plan with the subjects and discussed HSRB-recommended alterations to the ICF, inserted or crossed out language to reflect these alterations, and both he and the subject initialed the changes. This allowed the studies to proceed on schedule.

Dr. Carroll informed the HSRB and EPA staff that industry sponsors are concerned about the delays caused by the new review structure. He added that he also is concerned with the logistics of the situation and by the burden this structure places on EPA. He proposed as a more reasonable research cycle: 15 days for IRB protocol review and submission; 75 days for EPA and HSRB protocol reviews, including a HSRB meeting; 105 days for research and report submission; 75 days for subsequent EPA and HSRB reviews including a second HSRB meeting. This results in a total time of 270 days, which is the briefest timeframe appropriate to perform this research. The current procedure requires protocol revisions and re-reviews that place burdens on EPA staff, laboratories, and IRBs. Potential solutions to these issues include more lead time from sponsors, more research and regulatory staff, and more experience with the review procedure itself.

Dr. Fisher thanked Dr. Carroll for informing the Board about the challenges presented by the review process to sponsors and investigators, and asked Board members if they had questions for Dr. Carroll.

Dr. Sean Philpott asked Dr. Carroll to clarify who signed the new ICF. Dr. Carroll explained that subjects participating in the November 3, 2006 study at the marsh site signed the revised and original forms. Dr. Philpott commented that the HSRB did not receive documentation of tick handling training. Dr. Carroll assured him that he had documentation for training of all subjects and explained that Visit 1 for the subjects covered tick handling and the dosimetry study. Not all subjects who participated in the efficacy study participated in the dosimetry phase. He added that similar documentation was maintained for training subjects in aspiration of mosquitoes.

Drs. Fisher and Philpott requested clarification on whether the same subjects were involved in both the tick and mosquito studies. Mr. Carley explained that the same 12 subjects participated in the efficacy study for each of the 3 formulations of the product. Dr. Carroll offered to provide a flow chart that would document the movement of each subject through the study protocols. He added that he also would try to convince sponsors to combine the sub-reports into one report, to alleviate the problems and confusion arising from serial submissions of documents. Dr. Fisher stated that the HSRB would not make a recommendation concerning collapsing of studies, but would recommend a more accurate and informative portrayal of study participants.

Dr. Fisher questioned whether the participants in the study were representative of the general population, given that many of these people are from the same community, may have participated in a number of similar studies, and thus may be more experienced with applying insect repellents. Dr. Carroll answered that there is no historical art or practice in the field of dosimetry concerning how to define "representative." He sought information from investigators in the cosmetics industry and toxicology field to learn about dose monitoring. EMD-003 and EMD-004 enrolled subjects from a college-educated, field-oriented group. He acknowledged that these subjects may be more familiar both with the data collection process and with repellent application.

Dr. Philpott asked whether Dr. Carroll had monitored for arboviruses other than West Nile Virus, and whether the mosquitoes had been tested for the presence of transmissible viruses. Dr. Carroll responded that mosquitoes were not tested because this would have to be funded by study sponsors, but that material collected by abatement personnel was sent to the Centers for Disease Control and Prevention (CDC) for screening and no viruses were found.

Dr. Richard Sharp asked whether all protocol deviations had been reported to the IRB. Dr. Carroll replied that not all of the deviations had been reported. Dr. Chadwick expressed concern that crossing out a section on a consent form may be considered by some to be merely an editorial change; but, it is not acceptable according to regulations to do this without IRB approval. Under these circumstances, this was a minor change. However, he cautioned Dr. Carroll against repeating the activity. Dr. Carroll assured Dr. Chadwick he would not perform ad hoc revisions to a consent form. Dr. Carroll explained that in some cases, the changes requested from, and approved by, the IRB were not made on the forms the IRB returned as scans.

Dr. Lebowitz requested clarification of entry errors and whether these errors compromised the data. Dr. Carroll explained that entry errors refer to instances, such as incorrect crossing-out of mis-entered values. EPA staff could see the improperly entered value, and note that the replacement values were logical. Dr. Carroll added that during the tick data collection process, there was direct oversight by a trained technician of subject data collection and entry.

Dr. Lebowitz asked Dr. Carroll to explain the impact of a change of 1^{o}C above expected temperatures for two testing periods. Dr. Carroll explained that the original temperature values were based on his experience with a West Coast tick population, which is active in winter. These experiments used a Northeastern population that is more active at higher temperatures. No change in questing behavior was observed on the untreated arm when the temperature rose.

Dr. Lebowitz inquired why the two-way ANOVA analysis was not performed in the dosimetry phase to analyze within-subject variability and between-subject variability. Dr. Carroll explained that because the design was balanced, little information is lost by using the standard deviation of the grand mean instead of ANOVA. ANOVA was not performed because of a lack of time; however, the analysis was conducted on the aerosol study a couple of weeks later.

Dr. Philpott questioned why there were no data on dosimetry or efficacy for three subjects. Dr. Carroll explained that these subjects were either excluded for confidential reasons or participated only in the aerosol study. Dr. Fisher clarified that confidential refers only to information that could be used to identify a subject. The reason for exclusion can be given as long as it does not permit identification. Dr. Carroll remarked that he wished to avoid mentioning a class of people who might be excluded. Dr. Fisher stated that identifying a subject as a member of a class does not affect confidentiality or identification. Dr. Suzanne Fitzpatrick disagreed. Because this discussion took place at a public meeting, some of the original subjects might be attending and, because the subject pool was quite small, may have known who was excluded, and descriptions of reasons for exclusion could result in identification of subjects. Dr. Carroll offered to provide in the study report whether a person was excluded for personal reasons or voluntarily dropped out of the study. Dr. Fisher agreed that this would be useful, and thanked Dr. Carroll for his participation.

No further public comments were made.

Board Discussion

Scientific Considerations—EMD-003

Dr. Chambers reviewed the study EMD-003, in which two formulations (lotion and pump spray) containing the active ingredient IR-3535 were tested for the ability to repel ticks according to the protocol presented and modified, based on suggestions and input from EPA and the HSRB, by Carroll-Loye Biological Research, Inc. As suggested by the HSRB, passive dosimetry experiments were used to determine the amount of product typically used by consumers. This dose was calculated using the grand mean of 12 subjects tested and was used as

the dose for the repellency tests for each product. The dosimetry protocol was common for this and the mosquito repellency experiment, EMD-004.

The EMD-003 protocol was performed in a laboratory setting with only minor deviations, none of which affected safety or the quality of the data. A sample size of 10 subjects was justified as leading to sufficient statistical power while exposing only a small number of people to risk. Laboratory-reared, disease-free ticks were first tested on the untreated limb to confirm normal questing behavior. The first confirmed crossing was used to calculate the CPT. This study identified a range of 5 to 12 hours with a mean CPT of 9.1 hours for lotion, and 6.5 to 12 hours with a mean of 12.1 hours CPT for spray. These values probably are conservative, because some subjects terminated the experiment before the first confirmed crossing.

EMD-003 met scientific criteria established by the HSRB. Existing data were not adequate to answer questions concerning efficacy for the new formulations, thus new studies involving human subjects were warranted. Potential benefits to this study include identification of repellents with greater efficacy and/or fewer drawbacks than products currently on the market. Risk was minimal because the tested products were of low toxicity and ticks were laboratory-raised and pathogen-free. The most likely risk was irritation from tick bites, but this risk was low because subjects were instructed to remove the ticks before bites occurred. EMD-003 met study design criteria, including a clearly defined purpose (test efficacy), and specific hypotheses and objectives.

The study enrolled suitable subjects and study investigators anticipated that the findings would be generalizable to the general population; however, there was some question of how representative the study population was of the general population. The inclusion and exclusion criteria were appropriate and study subjects were not members of vulnerable groups.

Concerning measurement criteria, the measurements were accurate, reliable, and appropriate to the questions asked. QA was addressed, although some issues arose in this area. Appropriate statistical methods were used to calculate the CPT with a range of variability. The data generated using these methods (such as mean with a range of variability) were suitable for use by EPA for making regulatory decisions. Measures of uncertainty were addressed using standard deviation. Laboratory experiments were appropriate for testing tick repellency. The study included a medical management plan and safety monitoring.

According to data presented at this meeting, the dosimetry study indicated that subjects used more of the lotion formulation than the pump spray formulation, but better tick protection was found for the pump spray formulation. Protection time may be less related to dose than to how long the product lasts before evaporation or product deterioration results in loss of efficacy.

Dr. Chambers concluded that the reported study EMD-003 is sufficiently sound from a scientific perspective to assess repellent efficacy of the lotion and pump spray formulations against ticks.

Dr. Fitzpatrick agreed with Dr. Chambers' conclusions. She clarified that the levels of active ingredient in the pump spray and lotion formulations differed and were in line with

observed protection times. She agreed that deviations from the protocol were minor and presented no risk to study participants. Deviations, such as entry errors, are common in field studies. She agreed that the sample was representative, within the confines of the exclusion criteria. The study population included people likely to use the products. The dosimetry experiments were a commendable attempt to introduce dosing precision to this field. Although the average consumer might use more product, this is not a cause for concern because the formulations are already known to be safe and efficacious; these studies simply clarify a time range of effectiveness.

Dr. Lebowitz noted that Drs. Chambers and Fitzpatrick satisfied his concerns about generalizability. His concerns about the use of the grand mean were reduced by EPA's explanation that a CPT range will be used to develop the use label, with appropriate statements about individual variability.

Dr. Carriquiry agreed with Drs. Chambers, Fitzpatrick, and Lebowitz. She clarified that the negative control referenced in the protocol is not a true negative control, and references to this should be removed from the report or language should be added to clarify this.

Dr. Fisher asked meeting participants if there were any dosimetry models concerning adequate methodology for insect repellents. Mr. Carley responded that these were the first repellency studies with a specific dosimetry phase. Traditionally, 1 gm/600 cm^2 is used as an approximate typical consumer dose. The result of the dosimetry phase of this study indicated a lower typical dose; the impact of this would be a more conservative estimate of protection time. Dr. Fisher suggested that EPA might wish to provide guidance concerning whether this was a valid way to determine dose.

Ethical Considerations—EMD-003

Dr. Philpott opened discussion of ethical considerations of EMD-003. He stated that the benefits to this study were clearly defined. There were no direct individual benefits, but there is a societal benefit arising from identification of a new repellent product. Individual risk was clearly defined and the protocol included adequate attempts to minimize risks associated with toxicity, reactions to the compound, exposure to insect-borne diseases, and other unanticipated events. The likelihood of adverse reactions was minimal, a medical management plan was in place, stopping rules were clearly defined, and laboratory-raised ticks were used.

The study population had clear inclusion and exclusion criteria, although this was a population of convenience, composed of study subjects who had participated in previous Carroll-Loye Biological Research, Inc studies, members of Dr. Carroll's department at the University of California (UC)-Davis, and people with an interest in entomology. This raised questions concerning the representativeness of the population and questions of vulnerability because Dr. Carroll is academically affiliated with the UC-Davis. However, efforts were made to minimize vulnerability were adequate. Clear exclusion criteria and interviews of subjects by Dr. Carroll to assess their motivation for participating minimized the vulnerability. Subjects were compensated at a rate of $15 per hour for their participation; this could amount to several

hundred dollars if subjects participated in dose and efficacy studies for both formulations. This was not considered to be unduly excessive compensation.

A significant concern is the alteration and use of the ICF prior to IIRB approval. Although the intent was to improve the informed consent process and did not impede the process or harm participants, this was nonetheless a regulatory violation and Dr. Carroll should review IRB protocols and procedures. The study was in compliance with the criteria of 40 CFR 26 Subparts K and L and all necessary documents for review were submitted.

Dr. Fish agreed that all ethical concerns had been addressed. She added that because this is a new procedure for researchers and registrants, researchers should consider reviewing IRB requirements. Regulatory breaches in the protocol occurred; although no harm resulted, these were nonetheless breaches. EPA should consider requiring training in human subject protection.

Dr. Sharp clarified the two deviations from standards of clinical research ethics. First, minor protocol deviations and changes to ICFs occurred, but did not compromise subject protection. Second, the failure to report these deviations to the IRB perhaps presents a larger problem. Only the IRB can decide if an infraction is minor or requires corrective action, such as additional training or auditing. Dr. Fitzpatrick remarked that regulations require that deviations be "reported in a timely manner," which could mean 3 months for a minor deviation (based on Food and Drug Administration FDA practices). Dr. Fish countered that the IRB might wish deviations to be reported sooner. Dr. Fisher clarified that although the changes occurring during this study they did not result in harm, such changes could be harmful in other circumstances; the HSRB does not wish to downplay the potential seriousness of deviations of this sort.

Dr. Fisher presented the conclusion of the HSRB discussion of EMD-003:

1. Dr. Carroll and Mr. Carley adequately answered HSRB questions about dose, variability, and subjects. The HSRB consensus is that the data were valid and could be used for the indicated purpose.
2. Concerning ethics, some deviations occurred but did not place subjects at risk. The Board recognized that many deviations were introduced to provide more protection.

The Board discussed whether to recommend EPA develop a policy that investigators demonstrate ethics training similar to National Institutes of Health (NIH) policies. Dr. Chadwick stated that in his opinion, the Board should strongly recommend that EPA consider requiring ethics and human protection training to those investigators performing human subjects research.

Mr. Carley asked the Board for clarification. Application forms sent to the IIRB included responses to questions concerning the investigator's training in human studies and ethical standards. He asked whether this was adequate or if EPA should develop its own requirements and training. Dr. Fish added that not all IRBs ask whether investigators have been trained in human subject protection; NIH and a few other sources of federal funding require training. Dr. Fitzpatrick noted that NIH requires training to receive funding. If EPA does not fund a study, it may have less authority to require investigator training. Dr. Fisher summarized that the Board could recommend that EPA develop guidelines to ensure adequate training of investigators in

human research protection, rather than relying on IRBs. EPA also should determine the content of required training based on models such as those used by NIH.

Dr. Kim raised a technical issue concerning data analysis of EMD-003 and EMD-004. He commented that the CPT was determined as time to event (tick crossing or mosquito landing). However because some subjects dropped out before the event occurred, the actual time to event was not available. The investigators assumed that the true CPT would be longer than the time to drop out, but this may not be a valid assumption. He suggested that the investigators consider using the Kaplan-Meier estimate, which will give a correct unbiased median estimate of CPT along with the appropriate standard deviation, which will be much larger than what was reported in the study. The Kaplan-Meier estimate also can account for censored data, such as loses from the sample before the final outcome is observed. Dr. Fisher requested that information regarding the Kaplan-Meier estimate be forwarded to Dr. Lewis, who will forward it to EPA staff.

Scientific Considerations—EMD-004

Dr. Chambers reviewed the protocol, EMD-004, a field study in which the active ingredient IR-3535 in two formulations was tested for the ability to repel mosquitoes according to the protocol presented and modified, per EPA and HSRB input, by Carroll-Loye Biological Research, Inc. Data were reported for the pump spray and lotion formulations; the aerosol formulation would be presented at a later date. The formulations were made according to Good Manufacturing Practices and laboratory experiments performed using Good Laboratory Practices. The dosimetry phase was performed as reported and discussed for EMD-003.

EMD-004 was a field study conducted according to approved protocols with only very minor deviations, none of which affected the quality of data or compromised the safety of the subjects. Two locations in California were used, dense forest and moist pasture/marsh, which had differences in the composition and relative abundance of mosquito species. Neither site showed evidence of West Nile Virus.

A sample size of 10 subjects per product was justified as generating sufficient statistical power while exposing only a small number of people to potential risk. Each subject had one limb treated and the remaining limbs covered with impervious material. Two experienced persons served as negative controls (no repellent product) to confirm mosquito biting pressure and biting pressure was maintained throughout the period of the study; which was defined as at least one landing with an intent to bite (LIBe) or one LIBe per minute. Experimental subjects worked in pairs to monitor the LIBe during 1-minute intervals occurring each 15 minutes until the first confirmed LIBe was determined and stopping rules were applied. The CPT was calculated as the mean CPT of all participants for each product. The mean CPTs for the lotion were 7.3 hours for forest and 8.5 hours for marsh. Mean CPTs for the pump spray were 7.1 hours for forest and 8.4 hours for marsh. The calculated CPTs likely are conservative because a number of subjects reported no LIBes and some terminated the experiment before the first confirmed LIBe.

EMD-004 met general scientific criteria and had a clear scientific question—testing the efficacy of IR-3535 in repelling mosquitoes. Existing data were not adequate to answer

questions of efficacy of the new formulations. Therefore a new study involving human subjects was necessary. The potential benefits of the study included identification of an effective repellent with greater efficacy. Risk was minimal because the formulation products had low toxicity, mosquitoes were aspirated before they could bite, and test sites had no evidence of West Nile Virus.

The study design criteria were met. The study purpose was clearly defined, there were specific objectives and hypotheses, and an adequate sample size was used. There was justification for selection of the target population, which was appropriate and reasonable and met appropriate inclusion and exclusion criteria; vulnerable group subjects were not used.

Measurements were accurate, reliable, and appropriate to the question being asked. QA issues were addressed. The statistical methods used to calculate the CPT with a range of variability were appropriate. Field experiments were appropriate and the study included a medical management plan and safety monitoring.

Dr. Chambers concluded that EMD-004 was sufficiently sound from a scientific perspective to assess mosquito repellent efficacy of two formulations containing IR-3535.

Dr. Lebowitz agreed that the review was accurate. He had concerns about statistical questions, generalizability, and the number of subjects used. He stated that despite some shortcomings and deviations from protocol, the results could be used for the purposes suggested. Dr. Lebowitz concluded that the study was sufficiently sound to assess the repellant efficacy of the formulations tested against mosquitoes.

Dr. Kim agreed that the study was sound, but there were problems with the methods used to define the CPT, especially given the subject drop-out rate and methods used to estimate CPT for these subjects. The methods used would overestimate the repellency of the formulations and would artificially reduce the standard deviations. Using the Kaplan-Meier estimate would give a correct unbiased estimate of the median CPT and standard deviations larger than those reported, which would affect the label EPA develops for this product, because standard deviation is used to determine a CPT range. He expressed disappointment that no statistician at EPA had reviewed the data.

The Board discussed the statistical analysis method used in the study. Dr. Kim argued that the current protocol included data that did not exist (such as CPT, if the subject left before a mosquito landed), which could lead to underestimated standard deviations, and has implications for the product label. Dr. Fish questioned whether this was a standard method in repellant studies for measuring efficacy or determining time to a confirmatory event. If the same method is used in all studies, the impact should be the same and the relationship between different products remains constant. Dr. Kim pointed out that the degree of data censoring varies between studies. Thus there would be an impact on relative comparisons. Using the Kaplan-Meier estimate to calculate the median and standard deviation is appropriate when data that does not exist is imputed. Using the current approach results in biased means and standard deviations. Dr. Carriquiry agreed that re-analyzing the data using the Kaplan-Meier estimate likely would

result in large standard deviations. The practical consequence of this is wide confidence intervals, which will negatively impact efficacy estimates.

Dr. Fisher concluded that the Board would not reject the data, but would include in its recommendations that EPA should be aware that using arithmetic mean and standard deviation to determine the CPT is incorrect, and should consider different ways to determine mean and standard deviation. This comment is applicable to both EMD-003 and EMD-004. Mr. Carley stated that this data was analyzed in accordance with EPA guidelines; changes may be needed but should not affect this study. Dr. Fisher remarked that introducing new analysis methods could affect EPA's ability to compare products and deliver information to consumers concerning product performance relative to other products. She agreed, however that EPA should be given information about different statistical analysis techniques from Drs. Kim and Carriquiry and should consider applying these techniques to future studies. Mr. Jordan agreed with Dr. Fisher's suggestion and stated that EPA is trying to move toward more sophisticated ways of analyzing data. EPA follow-through on this advice is challenging because their database contains studies performed over decades ago with different designs and ways of calculating CPTs. EPA needs to balance regulatory considerations of label value based on different statistical approaches.

Dr. David Bellinger inquired whether the Board wished to revise the scientific criteria to include specification of the sampling frame (such as, definition of eligible subjects based on inclusion and exclusion criteria) used to enroll subjects; the current report does not describe the population from which subjects were drawn. Dr. Fisher agreed that definition of eligible subjects and sampling frame would strengthen justifications for generalizability and should be included in the report.

Dr. Fisher summarized the Board's discussion of the scientific criteria for EMD-004:

1. EMD-004 met scientific criteria with some minor deviations.
2. The Board had some concerns with respect to data usability, given the statistical methods used to analyze the data. EPA should consider alternate ways to analyze and evaluate the data. The Board is aware that EPA must consider relevance to other studies and how changes would affect consumer information.
3. The Board recommended inclusion of a description of the sampling frame and definition of eligible subjects to help justify subject generalizability.

Ethical Considerations—EMD-004

Dr. Philpott opened the ethics discussion by noting that ethics considerations for EMD-004 were similar to those of EMD-003. EMD-004 has similar societal benefits but no direct individual benefits. Clear stopping rules and a medical management plan were in place to protect subjects. Two anticipated risks to subjects are reactions to the compound (unlikely because of the toxicity profile of the active ingredient and history of its use in Europe) and risk of exposure to arboviruses. This risk was mitigated by the plan to conduct the trial only in a region with no evidence of West Nile Virus or Eastern Equine Encephalitis for one month, based on monitoring of chicken sentinels. A deviation to this protocol was the report of a single case of West Nile Virus in a single flock prior to the trial. The justification to continue was that the

chicken was not geographically close to the study site. In CDC's opinion, the West Nile Virus season was over in this region. However the geographical location of the flock site relative to the test site was not clear. The Board recommended reporting this as a potential deviation.

Concerning the study population, there are some questions as to whether this is a representative sample. Vulnerability issues also are a concern because some subjects may have had ties to Dr. Carroll, but as with EMD-003, sufficient safeguards were in place to eliminate coercion and vulnerability fears. Compensation for the subjects was not considered unreasonable. In accord with 40 CFR 26 Subparts K and L, no children or pregnant or nursing women were included in the study.

Two deviations exist concerning modification of the ICF approved on September 12, 2006. The first is the unapproved modification and use of the ICF, the second is the failure to report this deviation to the IIRB, although questions of timeliness of reporting have been raised. With respect to the EPA charge, EMD-004 is not unethical and comports with 40 CFR 26 Subparts K and L.

Dr. Chadwick commented that the charge asks if the protocol is in substantial compliance with applicable statutes. EPA needs to define "substantial" and determine the level of noncompliance it is willing to tolerate.

Dr. Fisher added that the detection of West Nile Virus in a sentinel flock is a QA issue that should have been reported to the IRB before the experiment began, although she agreed with CDC's opinion regarding subject safety. She agreed that the study presented no substantial ethical problems and subjects were not exposed to unacceptable risk or an increase in risk by these deviations.

Insect Repellent Efficacy Protocol SCI-001

Introduction

Mr. Carley and Mr. Kevin Sweeney (OPP, EPA) presented EPA's science and ethics reviews of protocol SCI-001, a proposal to field test mosquito repellency for four EPA-registered formulations containing DEET. These reviews were December 30, 2006, and were based on initial protocol submission as supplemented by additional documents received by December 13, 2006. A further revised version of the protocol, with IRB approval and revised ICF (and supporting correspondence) was received on January 3, 2007. SCI-001 is adapted from and similar to EMD-004, which was previously approved by the HSRB.

Scientific Considerations

Mr. Sweeney presented the science assessment of SCI-001. He explained that the objectives of this study are to test the mosquito repellent efficacy characteristics of three test materials, to compare them to one another, reinforce measurements of time for which they are effective, and to contrast them with the U.S. military issue topical insect repellent. Test Material #1 is LipoDEET, which contains 30% DEET that has lipid spheres and inhibits evaporation,

improved field, and reduced plasticizing and odor. Test Material # 2, Coulston's Duranon, is 20% DEET in a controlled-release, low-odor formulation. Test Material #3 is Insect Guard II, which contains as active ingredients 17.5% DEET, 5% N-octyl bicycloheptane dicarboximide (synergist), and 2.5% Di-n-propyl isocinchomerate (fly repellent). Test Material # 4, 3M Ultrathon (military issue repellent), contains 34.34% DEET in a polymer-based lotion to extend efficacy and reduce plasticizing.

This study was similar to EMD-003 and EMD-004 in terms of the dosimetry phase, efficacy measurements (time to "first confirmed landing with intent to bite"), and training of subjects in aspirating mosquitoes before they bite. The field conditions and timing of exposure also were similar (subjects work in pairs with 2 assistants to aspirate mosquitoes, and both treated and untreated subjects would be exposed to the mosquitoes for 1 minute every 15 minutes). The field testing sites are the California Central Valley or Florida Keys, with expected wild mosquito populations of *Aedes vexans, Ochlerotatus melanimon, O. taeniorhynchus, and Culex pipens*. The test results would be analyzed using unspecified statistics. Measurements would be reported with 95% confidence intervals of the mean and associated standard deviations. The efficacy of each treatment would be compared to that of Ultrathon. The sample size reflects a compromise between financial and ethical concerns, although it is difficult to pre-determine sample size without knowing the distribution of outcome values. EPA guidelines recommends 6 replicates, which is considered sufficient to show statistical significance at $P<0.05$.

EPA recommended changes to the protocol including developing a full description of the statistical analysis plan to compare means and assess within-treatment variability, and to define a testable hypothesis. If these revisions are completed, this protocol likely would yield scientifically reliable information and will satisfy the scientific criteria recommended by the HSRB, namely, producing important information that cannot be obtained except by research with human subjects, and having a clear scientific objective, and a study design that should produce adequate data to test the hypothesis.

Dr. Chambers questioned whether the study would compare the same amount of active ingredient or the same amount of material applied. Mr. Carley responded that the dose rate in the efficacy phase would be determined by a preliminary dosimetry phase. The grand mean of the subject mean will be calculated to obtain a standard dose for each product. These could be different for each product, resulting in variation in the DEET dose. Mr. Sweeney added that the DEET dose likely would be reported.

Dr. Fisher commented that to quantify the CPT, if subjects can drop out of the study at will, criteria will be needed to establish how long a subject must remain in the study to use their data, or if data from another subject can be substituted. Subject drop-out can influence the confidence interval. She also commented on the lack of dosimetry standards in the field, and asked whether the dosimetry method employed in EMD-003 and EMD-004 was satisfactory. If the dose is based on how much product the person applies, this could lead to confusion concerning how to compare the formulations with different amounts of DEET. Mr. Carley replied that the dosimetry phase would help to determine the typical consumer dose for each formulation. Subjects would be instructed to apply the product until they believe they have achieved complete coverage, and, because different formulations have a different feel, different

amounts likely would be applied. Dr. Fisher commented that this emphasizes how experienced subjects, or knowledgeable subjects, may not be representative of the general population in terms of product use.

Ethical Considerations

Mr. Carley presented the ethics assessment of SCI-001. The proposed study would test the field efficacy of 3 registered test formulations and one 'comparison article', all containing the active ingredient DEET as a mosquito repellent. Demonstration of long-term efficacy for the test products may lead to more attractive alternatives to the comparison article, which is found unpleasant by many users. The military issued Ultrathon is not used as widely as it should be because of these unpleasant characteristics. If the other formulations are found to be as effective as Ultrathon, a potential societal benefit lies in the increased use by those at risk for arthropod-borne diseases, such as members of the military.

Subjects will be recruited among "communities of friends, neighbors and scientists" near the investigator's laboratory, excluding students or employees of the investigator, or members of vulnerable populations, such as children and pregnant or nursing women.

Risks include possible irritation, headache, dizziness or temporary stomach distress from exposure to the test materials, and exposure to biting arthropods and arthropod-borne disease. These risks were are considered small because the materials have low acute and chronic hazard profiles, the research had been designed to minimize exposure, subjects were trained to aspirate mosquitoes before they bite, and field testing would be performed in areas free of West Nile Virus. The risk-benefit ratio is acceptable, because although there is no direct benefit to subjects, there is a low level of risk that is acceptable in view of the expected societal benefit of the identification of alternative, effective, long-lasting mosquito repellents.

The IIRB reviewed and approved the protocol and informed consent materials. The description of the recruiting and consent processes has been deemed satisfactory and the IRB-approved ICF is included in the protocol; a few editorial changes are needed in the ICF. Methods have been proposed for ensuring subject privacy. Subjects would be free to withdraw at any time, and medical care for research-related injuries would be provided at no cost to the subjects.

The primary ethical standards applicable to this research are 40 CFR 26, Subparts K and L. An evaluation of how this protocol addressed the requirements of these standards and the additional criteria recommended by the HSRB appears as Attachment 1 to the EPA Review. Further revisions to the protocol include provision of the fax and set-up form cited in the IIRB/Carroll correspondence; correction of the erroneous reference in the ICF to EMD as a sponsor and in §10.1 to gauze bracelets in the dosimetry phase; deletion of the reference in §12 to conducting research in the Florida Keys or an explanation in §9.1.5 describing how subjects will be recruited in Florida; and provision of documentation of all calculations of subject skin area and of individual doses in the efficacy phase.

This protocol was in compliance with ethical standards § 26.1111, 26.1116, 26.1117, 26.1125, 26.1203, all elements of the National Academy of Sciences (NAS) recommendation 5-1, and all elements of NAS recommendation 5-2. If further revised as suggested, protocol SCI-001 would meet the applicable requirements of 40 CFR part 26, subparts K and L. The various parts of the protocol need to be consolidated, proofread, and submitted as a single document for review.

Public Comment

Dr. Scott Carroll of Carroll-Loye Biological Research, Inc.

Dr. Carroll explained that SCI-001 was developed while collecting data for EMD-003 and EMD-004. Development of the protocol required a great deal of input from EPA, which Dr. Carroll would like to be able to reduce in the future.

Concerning the statistical analysis, Dr. Carroll's goal, based on the sponsor's wishes, is to determine how each formulation compares to Ultrathon. This involves a pairwise comparison approach and comparative survival analysis was determined to be appropriate, based on Dr. Carroll's discussions with a colleague familiar with this type of analysis. The data would be used to provide a value to justify label changes by EPA and to provide the military with information they can use to identify a suitable and effective replacement for Ultrathon. Concerning subjects who dropped out of EMD-003 and EMD-004, this issue arose because the products remained efficacious for longer than anticipated, and subjects were thus not informed that the study could last for more than 7 hours. For SCI-001, Dr. Carroll has proposed increasing compensation to $20 per hour and informing the subjects that they may be in the field for more than half a day (12 hours). If drop-outs continue to be a problem, the approach as described previously by HSRB member Dr. Kim would be used to analyze the data.

Dr. Carroll discussed the issue of subject recruitment in Florida from a pool of vector professionals. This group may not constitute a representative sample. The Florida site was chosen as an alternate for when California is off-season. Dr. Fisher inquired why, if for any given month there are appropriate sites around the country for this experiment, there was a rush for the HSRB to review this protocol. Dr. Carroll replied that since the advent of the new review system, many sponsors were concerned that the process would lead to delays in registration of products. Dr. Fisher commented that this issue had been raised at a previous meeting, and the HSRB had asked EPA to provide a justification for the urgency of review.

In response to Dr. Fisher's question concerning substitution of subjects, Dr. Carroll explained that this would incur additional expenses given the increased exposure time needed. Dr. Fisher replied that the experiment did not appear to be costly and wondered how substantial the increase in cost would be to use a substitute. She also commented on the lack of criteria for establishing how long a subject needs to remain in the field to include their data in the analysis. Dr. Carroll responded that for this protocol, subjects would be asked to remain in the field for 12 hours. Although EPA approved a claim of 4 hours of efficacy for the products being tested, this value is based on extrapolation from other formulations with similar percentages of DEET.

The manufacturers believe the products would last longer. Additionally, Ultrathon has previously been demonstrated to last 12 hours.

Dr. Chambers commented that substitution also would require inclusion of untreated controls, which may present an ethical issue. Dr. Fitzpatrick suggested that it might be more effective to include more subjects than called for in the original protocol. Dr. Carroll agreed, but added that it has been difficult to increase the sample size from 6 to 10.

Dr. Fish asked why the inclusion criteria for this protocol specified an age range of 18 to 55 years, compared to the EMD-003 and EMD-004 protocols, which specified older than 18 years. Dr. Carroll explained that the upper limit of 55 years was recommended by the CDC, which considers West Nile Virus to present a more serious health risk for those over the age of 55. Dr. Fish inquired about whether a sentence in the protocol stating that "subjects may obtain data" meant that the subjects could remove their data or obtain a copy. Dr. Carroll replied that subjects would be given a copy of their data. Dr. Fish commented that the ICF stated that the amount of product used would not be greater than one-quarter teaspoon and asked if this could be confirmed prior to the dosimetry phase. Dr. Carroll agreed that this statement should be changed to read "approximately one-quarter teaspoon."

Dr. Krishnan inquired if the experiments would run for 12 hours per day, given the claims of up to 12 hours of effectiveness for Ultrathon. Dr. Carroll explained that individual subjects would be occupied for more than 12 hours because of travel to and from the research site. He suspected that the products likely would last between 8 and 12 hours. He stated that he intends to explain to the subjects that the products could be efficacious for more than 12 hours; this is the rationale for the higher rate of compensation. Dr. Krishnan inquired if the results concerning variability from the EMD-003 and EMD-004 studies would be used to estimate sample size for this protocol. Dr. Carroll replied that this presented a good basic research question, although probably not one appropriate for the sponsors to pursue.

Dr. Krishnan remarked that he was struck by errors that the IRB did not catch regarding this protocol. Dr. Carroll stated that, in the past, he has noticed that the IRB did not always thoroughly examine the materials he provided to them. However he is now observing that this IRB appears to be reviewing materials more thoroughly.

Dr. Lebowitz questioned whether other arthropod-borne diseases, such as Dengue Fever or Eastern Equine Encephalitis could be present at the test site and asked if Dr. Carroll would use the same precautions outlined in EMD-003 and EMD-004 to reduce the risk of exposure to these diseases. Dr. Carroll explained that those precautions would be used. Dr. Lebowitz inquired if the timeframe for exposure would include times at which mosquitoes with different habits (i.e., night active or daylight active) were present. Dr. Carroll responded that he could expose subjects at times during which mosquitoes found at that site are most active. Another approach is to divide the 12 hours of exposure time to incorporate different times of day.

Dr. Kim commented that because there was no hypothesis concerning expected differences between the formulations, an estimate of the needed sample size could not be made. Dr. Carriquiry agreed that the justification for a sample size of 10 was not adequate from a

statistical perspective. The justification for not increasing the sample size above 10 is not compelling.

Board Discussion

Scientific Considerations

Dr. Krishnan stated that the SCI-001 protocol was valid and likely to generate valid data. It is unclear whether information on comparative efficacy can be obtained. EPA does not permit statements of comparative efficacy, so the rationale for this research was questionable. A clearer statement of how comparisons would be made is needed. It is apparent from the documentation that the formulations have low chronic toxicity and the typical consumer dose is likely to be below toxicity benchmarks. Nonetheless, toxicity values are needed. Dr. Krishnan expressed surprise and concern that the response variability from EMD-003 and EMD-004 would not be used to determine sample size for SCI-001. He also expressed concern about the proposed data analysis.

Dr. Carriquiry commented that the protocol needs significant revision as related to statistical analysis. The proposed calculation of means makes comparisons across products difficult; an exponential model might be more suitable. She also expressed concern that the subjects were not representative of typical users. She agreed that with modifications, the protocol would generate valid data.

Dr. Fisher summarized the Board's comments on SCI-001. Given that subjects would be asked to remain in the field for up to 12 hours, the Board should consider a risk-benefit analysis in terms of the number of subjects tested, so that if too many drop out before evidence of loss of product efficacy, substitutions can be made. The Board also recommended the investigator consider using the Kaplan-Meier estimate for endpoint analysis as suggested by Dr. Kim for EMD-003 and EMD-004. A rationale and appropriate analysis for the endpoint chosen should be developed.

Dr. Fisher discussed differences between training subjects to aspirate mosquitoes and training to criteria for subjects recording data. Standard practice is to train to criteria before the study begins. The protocol also should provide a more thorough explanation of how the reviewers can be confident of the reliability of self-report by subjects.

The Board believed that, from a statistical perspective, there was no evidence that comparative efficacy is possible. There was no clear hypothesis, so power analysis would be difficult. However, if a hypothesis was developed, the protocol could provide data that could be used to determine variability and estimate the needed sample size.

Because study participants were drawn from a population of friends and colleagues of the investigator, they are unlikely to represent a random sample. A response bias could occur based on subjects' familiarity with the products. The protocol should address the need to obtain a random, naïve sample of participants.

Dr. Fish expressed concerns about using the grand mean of means and asked whether the Board should consider recommending the investigator use the lower quartile instead of midpoint for determining dose. Dr. Lebowitz commented that there is a tendency to use geometric means to normalize data, but investigators should not assume *a priori* an appropriate distribution of data for use of this approach. Use of the Kaplan-Meier estimate for statistical analysis should be considered. Dr. Chambers asked whether using the lower quartile to determine dose for efficacy would hinder the ability to compare the results of this study to other studies. Dr. Fish replied that dosimetry experiments for this field were first performed in protocols EMD-003 and EMD-004, so consistency would be an issue no matter which approach is used to determine dose. Dr. Fisher suggested that the investigator perform both analyses. It may be necessary for EPA to use the results of traditional analyses for comparisons, but EPA also should collect results from different analyses for possible use in the future.

Ethical Considerations

Dr. Sharp thanked Mr. Carley for his review of the ethical considerations of this protocol and commended him on the level of data provided. He commented that the existence of multiple versions of the same trial made tracking and review difficult. Dr. Sharp noted four deficiencies in the protocol:

1. The protocol does not give an adequate description of recruitment of controls. Assuming that targeted calls would be made to potential volunteers, or flyers will be posted seeking volunteers, these materials (including scripts for the calls) should be submitted to the IRB.

2. The description of risk attributed to DEET exposure in the ICF refers to sprays containing alcohol. Lotions are used in the study; thus, this statement should be corrected.

3. The ICF is inapplicable to controls and should be corrected.

4. The ICF indicates that 40 subjects would participate. This should be changed to "48 or more subjects" to avoiding capping the number of permitted subjects at too low a level to allow appropriate statistical analysis.

Dr. Sharp also commented that he had concerns about the quality of the IRB review in general. In addition, the training, experience and qualification of IRB members should be included in each submission.

Dr. Philpott agreed that the proposed number of subjects should be changed to reflect a possible need for more subjects. He also recommended including a description of procedures to monitor for arthropod-borne disease other than West Nile Virus, both in the protocol and in the ICF.

Dr. Fisher summarized that more information was needed concerning recruitment of controls, such as a script for telephone calls. A different ICF also will be needed for the controls.

The error concerning risk based on alcohol-containing formulations should be corrected. The protocol and ICF also should describe with greater accuracy the need for a specific number of subjects. The risk to controls concerning diseases other than West Nile Virus should be more clearly explained.

Dr. Fisher suggested that the HSRB consider comments addressing the adequacy of the IRB information received by EPA, and recommended that EPA remind the HSRB about the availability of information concerning the IRB's qualifications.

Dr. Lewis thanked Board members, EPA staff, and Dr. Carroll for their participation. He informed Board members that the next HSRB meeting is scheduled for April 18-20, 2007, at EPA's Potomac Yard facility. The next teleconference is planned for March 22, 2007, at approximately 1 p.m. EDT for the Board to review its draft report from today's meeting. He will send Board members a list of dates for meetings and teleconferences planned for 2007.

Dr. Fisher adjourned the meeting.

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 for 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	List of 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
Rochester, MN

Members

David C. Bellinger, Ph.D.
Professor of Neurology
Harvard Medical School
Professor in the Department of Environmental Health
Harvard School of Public Health
Children's Hospital
Boston, MA

Alicia Carriquiry, Ph.D. **
Professor
Department of Statistics
Iowa State University
Ames, IA

Gary L. Chadwick, PharmD, MPH, CIP
Associate Provost
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

Richard Fenske, Ph.D., MPH *
Professor
Department of Environmental and Occupational Health Sciences
University of Washington
Seattle, WA

Susan S. Fish, PharmD, MPH
Associate Professor, Biostatistics & Epidemiology
Boston University School of Public Health
Co-Director, MA in Clinical Investigation
Boston University School of Medicine
Boston, MA

Suzanne C. Fitzpatrick, Ph.D., DABT
Senior Science Policy Analyst
Office of the Commissioner
Office of Science and Health Coordination
U.S. Food and Drug Administration
Rockville, MD

KyungMann Kim, Ph.D., CCRP
Professor and Associate Chair
Department of Biostatistics & Medical Informatics
School of Medicine and Public Health
University of Wisconsin-Madison
Madison, WI

Kannan Krishnan, Ph.D.
Professor
Département de santé environnementale et santé au travail
Faculté de médicine
Université de Montréal
Montréal, QC Canada

Michael D. Lebowitz, Ph.D., FCCP
Professor of Public Health & Medicine
University of Arizona
Tucson, AZ

Lois D. Lehman-Mckeeman, Ph.D. *
Distinguished Research Fellow, Discovery Toxicology
Bristol-Myers Squibb Company
Princeton, NJ

Jerry A. Menikoff, M.D. *
Associate Professor of Law, Ethics & Medicine
Director of the Institute for Bioethics, Law and Public Policy
University of Kansas Medical Center
Kansas City, KS

Sean M. Philpott, Ph.D.
Associate Professor of Clinical Ethics
Albany Medical College
Associate Director
Alden March Bioethics Institute
Albany Medical Center
Albany, NY

Richard Sharp, Ph.D.
Assistant Professor of Medicine
Center for Medical Ethics and Health Policy
Baylor College of Medicine
Houston, TX

* Not in attendance
** Participated via phone

Attachment B
Federal Register Notice Announcing Meeting

Human Studies Review Board; Notice of Public Meeting

[Federal Register: December 28, 2006 (Volume 71, Number 249)]
[Notices]
[Page 78200-78202]
From the Federal Register Online via GPO Access [wais.access.gpo.gov]
[DOCID:fr28de06-73]

ENVIRONMENTAL PROTECTION AGENCY
[EPA-HQ-ORD-2006-0998'; FRL-8262-7]

Human Studies Review Board; Notice of Public 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 reviews of human subjects' research.

DATES: The public meeting will be held January 24, 2007 from 8:30 a.m. to approximately 5:30 p.m., Eastern time.
LOCATION: Sheraton Crystal City Hotel, 1800 Jefferson Davis Highway, Arlington, VA 22202. The telephone number for the Sheraton Crystal City Hotel is 703-486-1111.
MEETING ACCESS: Seating at the meeting will be on a first-come basis. To request accommodation of a disability please contact the person listed under

[[Page 78201]]

FOR FURTHER INFORMATION CONTACT at least 10 business days prior to the meeting, to allow EPA as much time as possible to process your request.
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 Unit I.D. of this notice.

FOR FURTHER INFORMATION CONTACT: Any member of the public who wishes further information should contact Lu-Ann Kleibacker, EPA, Office of the Science Advisor, (8105R), Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460; telephone number: (202)564-7189; fax: (202) 564 2070; e-mail address: kleibacker.lu-ann@epa.gov. General information concerning the EPA HSRB can be found 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-2006-0998, by one of the following methods:
Internet: http://www.regulations.gov Follow the on-line instructions for

submitting comments.

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

Mail: Environmental Protection Agency, EPA Docket Center (EPA/DC), ORD Docket, Mailcode: 28221T, 1200 Pennsylvania Ave., NW, Washington, DC 20460.

Hand Delivery: The EPA/DC Public Reading Room is located in the EPA Headquarters Library, Room Number 3334 in the EPA West Building, located at 1301 Constitution Ave., NW, Washington DC. The hours of operation are 8:30 AM to 4:30 PM Eastern Standard Time (EST), Monday through Friday, excluding Federal holidays. Please call (202) 566-1744 or email the ORD Docket at ord.docket@epa.gov for instructions. Updates to Public Reading Room access are available on the website (http://www.epa.gov/epahome/dockets.htm).

Instructions: Direct your comments to Docket ID No. EPA-HQ-ORD-2006-0998. 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.

SUPPLEMENTARY INFORMATION:

I. Public Meeting

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, including such 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 http://www.regulations.gov index. Although listed in the index, some information is not publicly available, e.g., CBI or other information whose disclosure is restricted by statute. Certain other material, such as copyrighted 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. The EPA/DC Public Reading Room is located in the EPA Headquarters Library, Room Number 3334 in the EPA West Building, located at 1301 Constitution Ave., NW, Washington DC. The hours of operation are 8:30 AM to 4:30 PM EST, Monday through Friday, excluding Federal holidays. Please call (202) 566-1744 or email the ORD Docket at ord.docket@epa.gov for instructions. Updates to Public Reading Room access are available on the website (http://www.epa.gov/epahome/dockets.htm).

EPA's position paper(s), charge/questions to the HSRB, and the meeting agenda will be available by late December 2006. In addition, the Agency may provide additional background documents as the materials become available. You may obtain electronic copies of these documents, and certain other related documents that might be available electronically, from the regulations.gov website and the HSRB Internet Home Page at http://www.epa.gov/osa/hsrb/. For questions on document availability or if you do not have access to the Internet, consult the person listed under FOR FURTHER INFORMATION CONTACT.

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

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

a. Explain your views as clearly as possible.

b. Describe any assumptions that you used.

c. Provide copies of any technical information and/or data you used that support your views.

d. Provide specific examples to illustrate your concerns and suggest alternatives.

e. 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. To ensure proper receipt by EPA, it is imperative that you identify docket ID number EPA-HQ-ORD-2006-

[[Page 78202]]

0998 in the subject line on the first page of your request.

a. Oral comments. Requests to present oral comments will be accepted up to January 17, 2007. 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 email) to the person listed under FOR FURTHER INFORMATION

CONTACT no later than noon, Eastern time, January 17, 2007 in order to be included on the meeting agenda and to provide sufficient time for the HSRB Chair and HSRB Designated Federal Officer (DFO) to review the agenda to provide an appropriate public comment period. The request should identify the name of the individual making the presentation, the organization (if any) the individual will represent, and any requirements for audiovisual equipment (e.g., overhead projector, LCD projector, chalkboard). Oral comments before the HSRB are limited to five minutes per individual or organization. Please note that this limit applies to the cumulative time used by 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 these 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. Each speaker should bring 25 copies of his or her comments and presentation slides for distribution to the HSRB at the meeting. b. 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, Eastern time, January 17, 2007. You should submit your comments using the instructions in Unit I.C. of this notice. In addition, the Agency also requests that person(s) submitting comments directly to the docket also provide a copy of their comments to the person listed under FOR FURTHER INFORMATION CONTACT. There is no limit on the length of written comments for consideration by the HSRB.

E. Background

A. Topics for Discussion

The EPA will present for HSRB review the results of two completed insect repellent efficacy studies on which it intends to rely in making registration decisions. In addition, EPA will present for HSRB review a proposal for new research involving a field study to evaluate the efficacy of a mosquito repellent. The Board may also discuss planning for future HSRB meetings.

B. Meeting Minutes and Reports

Minutes of the meeting, summarizing the matters discussed and recommendations, if any, made 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 from the person listed under FOR FURTHER INFORMATION CONTACT.

Dated: December 21, 2006.

George M. Gray,

Science Advisor

[FR Doc. E6-22300 Filed 12-27-06; 8:45 am]

BILLING CODE 6560-50-P

Attachment C

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
HUMAN STUDIES REVIEW BOARD (HSRB)
PUBLIC MEETING

JANUARY 24, 2007*
SHERATON CRYSTAL CITY HOTEL
ARLINGTON, VA

HSRB Web Site: http://www.epa.gov/osa/hsrb/
Docket Telephone: (202) 566-1752
Docket number: EPA-HQ-ORD-2006-0998

8:30 a.m. **Introduction and Identification of Board Members**
Celia Fisher, Ph.D. (HSRB Chair)
8:45 a.m. **Welcome**
George Gray, Ph.D. (EPA Science Advisor)
8:55 a.m. **Opening Remarks**
Mr. Jim Jones (Director, Office of Pesticide Programs, [OPP], EPA)
9:05 a.m. **Meeting Administrative Procedures**
Paul Lewis, Ph.D. (Designated Federal Officer [DFO], HSRB, OSA, EPA)
9:10 a.m. **Meeting Process**
Celia Fisher, Ph.D. (HSRB Chair)
9:25 a.m. **Update on EPA Follow-up of HSRB Recommendations**
Mr. William Jordan (EPA, OPP)

Insect Repellent Completed Efficacy Studies EMD-003 and EMD-004
9:35 a.m. **Science and Ethics of Insect Repellent Completed Efficacy Studies EMD-003 and EMD-004**
Clara Fuentes, Ph.D. (OPP, EPA) and Mr. John Carley (OPP, EPA)
10:15 a.m. **Break**
10:30 a.m. **Public Comments**
11:00 a.m. **Board Discussion**

EMD-003.1 and EMD-003.2: Tick Repellency with Lotion and Pump Spray Formulations

a. Are these studies sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy of the formulations tested against ticks and mosquitoes?

b. Does available information support a determination that these studies were conducted in substantial compliance with subparts K and L of EPA regulations at 40 CFR part 26?

EMD-004.1 and EMD-004.2: Mosquito Repellency with Lotion and Pump Spray Formulations

a. Are these studies sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy of the formulations tested against ticks and mosquitoes?

b. Does available information support a determination that these studies were conducted in substantial compliance with subparts K and L of EPA regulations at 40 CFR part 26?

12:30 p.m. Lunch

Insect Repellent Efficacy Protocol SCI-001

1:30 p.m. Science and Ethics of Insect Repellent Efficacy Protocol SCI-001
Mr. Kevin Sweeney (OPP, EPA) and Mr. John Carley (OPP, EPA)

2:30 p.m. Public Comments

3:00 p.m. Break

3:15 p.m. Board Discussion

a. If the proposed research described in Protocol SCI-001 from Carroll-Loye Biological Research is revised as suggested by EPA, does the research appear likely to generate scientifically reliable data, useful for assessing the efficacy of the test substances for repelling mosquitoes?

b. If the proposed research described in Protocol SCI-001 from Carroll-Loye Biological Research is revised as suggested by EPA, does the research appear to meet the applicable requirements of 40 CFR part 26, subparts K and L?

4:30 p.m. Adjournment

* Please be advised that agenda times are approximate. For further information, please contact the Designated Federal Officer for this meeting, Paul Lewis via telephone: (202) 564-8381 or email: lewis.paul@epa.gov.