Minutes of the
United States Environmental Protection Agency (EPA)
Human Studies Review Board (HSRB)
June 23, 2010 Public Meeting
Docket Number: EPA-HQ-ORD-2010-0381
HSRB Web Site: http://www.epa.gov/osa/hsrb

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

Date and Time:	Wednesday, June 23, 2010, 10:00 AM – 5:20 PM (See *Federal Register* Notice – Attachment B)	
Location:	EPA, One Potomac Yard (South Bldg.), 2777 S. Crystal Drive, Arlington, VA 22202	
Purpose:	The EPA Human Studies Review Board provides advice, information, and recommendations on issues related to the scientific and ethical aspects of human subjects research.	
Attendees:	Chair:	Sean Philpott, Ph.D., M.S. Bioethics
	Vice Chair:	Janice Chambers, Ph.D., D.A.B.T.
	Board Members:	George C.J. Fernandez, Ph.D. Vanessa Northington Gamble, M.D., Ph.D. Sidney Green, Jr., Ph.D., Fellow, ATS Dallas E. Johnson, Ph.D. Michael D. Lebowitz, Ph.D., FCCP Jerry A. Menikoff, M.D. William J. Popendorf, Ph.D. Ernest D. Prentice, Ph.D. Virginia Ashby Sharpe, Ph.D. Linda J. Young, Ph.D.
Meeting Summary:	Meeting discussions generally followed the issues and general timing as presented in the meeting Agenda (Attachment C), unless noted otherwise in these minutes.	

Meeting Administrative Procedures

Mr. Jim Downing (Designated Federal Officer [DFO], Human Studies Review Board [HSRB or the Board], Office of the Science Advisor [OSA], U.S. Environmental Protection Agency [EPA or the Agency]) convened the meeting and welcomed Board members, EPA colleagues, and members of the public. He recognized and thanked new members Drs. Virginia Ashby Sharpe, George C.J. Fernandez, and José Manautou (absent). Dr. Sharpe is an ethicist for the Veterans Health Administration and a visiting scholar at Georgetown University; Dr. Fernandez is a professor and director of the Center for Research Design and Analysis at the

University of Nevada-Reno; and Dr. Manautou is an associate professor at the University of Connecticut's School of Pharmacy.

Mr. Downing announced that it would be the last meeting for Dr. Ernest Prentice, who has served on the HSRB since October 2007. In appreciation of his service, Mr. Downing presented him with a plaque from the EPA/OSA and a letter of thanks from EPA Administrator Lisa Jackson. In addition, Dr. Sean Philpott expressed his personal appreciation for Dr. Prentice's years of service to the Board. Dr. Prentice stated that he had enjoyed his tenure on the HSRB and will miss the Board's deliberations.

Mr. Downing noted that in his role as the DFO under the Federal Advisory Committee Act (FACA), he serves as liaison between the Board and EPA and is responsible for ensuring that all FACA requirements are met. The DFO must ensure that all appropriate ethics regulations are satisfied regarding conflicts of interest; Board members have been briefed on federal conflict of interest laws and have completed a standard government financial disclosure report. In consultation with the OSA deputy ethics officer and the Office of the General Counsel, Mr. Downing has reviewed the reports to ensure that all ethics requirements are met.

Mr. Downing informed the public that agenda times are approximate. Copies of the meeting materials and public comments will be available on www.regulations.gov. Following presentations, time has been scheduled for questions of clarification to EPA staff and the principal investigator and sponsors of the studies discussed. A public comment period will be maintained and remarks should be limited to five minutes. During Board discussions, if members require clarification from the public, they may request such information through the Chair or DFO. All background materials for the meeting will be available in the public docket and most documents are available also on the HSRB Website. Meeting minutes, including a description of the matters discussed and conclusions reached by the Board, will be prepared and must be certified by the meeting Chair within 90 days. The HSRB also will prepare a final report as a response to questions posed by the Agency that will include the Board's review and analysis of materials presented. EPA will announce the Board review and subsequent approval of the report through the *Federal Register*.

Introduction and Identification of Board Members

Dr. Philpott welcomed members of the public to the meeting and thanked the Agency and Board members for their service. He asked Board members to introduce themselves. He introduced Dr. Pai-Yei Whung (Chief Scientist, OSA), who offered welcoming remarks.

Welcoming Remarks

Dr. Whung welcomed the Board members and thanked them for offering their time to serve on the HSRB. She also welcomed the Board members on behalf of the EPA Science Advisor Dr. Paul Anastas who could not attend the meeting because he was in New Orleans working on tasks related to the oil spill. (Dr. Anastas was confirmed early in 2010, and joined the Agency as Assistant Administrator of the Office or Research and Development and the Science Advisor.) In Dr. Anastas' vision, he has highlighted the principles of the path forward for the

Agency, including innovation, sustainability, multi-disciplinary research in science, and scientific integrity. Dr. Whung noted her appreciation for the Board members' advice on human study matters. Today's meeting will consist of three primary subjects: two complete picaridin-based insect repellent studies, the Office of Pesticide Programs (OPP) revision of the Product Performance Test Guidelines, and an update on the status of the litigation against the EPA's Human Studies Rule.

Opening Remarks

Mr. William Jordan (OPP, EPA) observed that the agenda called for a presentation by Dr. Steven Bradbury, the new OPP director, but he could not attend. Mr. Jordan also pointed out that the former Office of Prevention, Pesticides and Toxic Substances had changed its name to the Office of Chemical Safety and Pollution Prevention (OCSPP) in an effort to reflect more accurately the work conducted. On behalf of Dr. Bradbury and OCSPP, he thanked the Board members for their assistance in ensuring that the research conducted on pesticides meets high scientific and ethical standards. He welcomed the new members, and expressed his hope that they would find the position interesting and challenging.

Mr. Jordan offered Dr. Bradbury's comments on the last agenda item, the report on recent developments in the lawsuit on EPA's human studies regulation. On June 18, 2010, EPA filed papers with the court in New York to settle the lawsuit, which challenged the regulation promulgated in 2006. The regulation instituted a number of significant new protections for human subjects in research. It extended the principles of the Common Rule to third party pesticide research involving intentional exposure of human subjects, prohibited research involving intentional exposure of children and pregnant and nursing women, and required the review of protocols for proposed research by EPA and the HSRB. When the lawsuit was filed in the spring of 2006, EPA defended against it by filing briefs and offering oral arguments in 2008. When Ms. Jackson took office in 2009, the Agency explored the possibility of settling the case. EPA took the position that the rule was legally, ethically, and scientifically sound; therefore, it held that the substance of the rule should be preserved while addressing the petitioners' concerns. The terms of the settlement agreement have successfully accommodated both perspectives. Since 2006, in partnership with the HSRB, EPA has shown that it is possible to conduct high quality scientific research with human subjects that is held to the highest ethical standards. The rigorous reviews conducted by EPA and the HSRB, as mandated by the rule, resulted in better science and stronger ethics in all of the new research conducted during the past four years. Investigators have learned how to document their research better and the quality of the protocols has improved dramatically; the Board's input also has improved EPA's reviews. In providing for the establishment of the HSRB, the rule has reassured the public that all pesticide research involving human subjects undergoes thorough independent and expert review.

EPA appreciates the work of the Board, particularly Drs. Philpott and Janice Chambers. Mr. Jordan thanked Dr. Prentice for his service and Mr. Downing for his work in managing the Board. He further thanked members of the public and noted that they could contact OPP staff with any questions. On behalf of Dr. Bradbury, he wished the Board a productive meeting.

EPA Follow-up on Previous HSRB Recommendations

Mr. Jordan observed that in October 2009, the HSRB reviewed two published studies on the effects on exposure to pyrethrins/pyrethroids on asthma and other allergies. The Board found that the studies were scientifically limited and identified further considerations that EPA should take into account when determining whether to cite the studies. EPA is completing a revised white paper addressing pyrethrins and pyrethroids that will summarize the studies, note their limitations, and cite the HSRB report; the conclusion of the paper was not affected by these studies. The Antimicrobial Exposure Assessment Task Force (AEATF) protocol to evaluate exposure from aerosol products has been modified to incorporate EPA and HSRB comments. The study will be executed soon, and a report on the completed research should be presented to the HSRB in 2011.

The HSRB also reviewed the protocols of two studies developed by Carroll-Loye Biological Research Inc. (CLBR): LNX-002 on field repellency of two picaridin formulations to biting flies, and LNX-003 on laboratory repellency of two picaridin formulations to two tick species. These protocols have been executed, and reports on the studies will be the subject of presentations at this meeting.

Completed CLBR Study LNX-002: Field Repellency of Two Picaridin-Based Personal Insect Repellents to Black Flies

Background

Mr. John Carley (OPP, EPA) described LNX-002, which was a field test in one habitat of repellency of two picaridin repellents against biting flies. Ten subjects were treated with each repellent on one arm at dose rates established in earlier LNX-001, with two untreated subjects included to confirm pest pressure. The test endpoint was the first confirmed landing with intent to bite (LIBe) for each subject.

The March 23, 2009 protocol was approved by the Independent Institutional Review Board (IIRB) in Plantation, FL, on March 24, 2009, and submitted to EPA by CLBR. EPA found the protocol acceptable with minor changes on May 18, 2009; in June 2009, the HSRB reviewed the protocol, agreeing with EPA but suggesting that testing be conducted only with black flies or midges (the original protocol had identified other types of biting flies). The protocol was amended (Amendment 1) to address EPA and HSRB comments, and was approved by IIRB on August 18, 2009, and by the California Department of Pesticide Regulation (CDPR) on September 14, 2009. HSRB leadership decided that the changes were not significant enough to require another review by the Board. EPA had consulted the Board because at the June 2009 HSRB meeting, a study on the same two repellents run by a different laboratory showed a different result for dose determination of the cream product. The study sponsor therefore asked that the protocol be modified to include 15 additional subjects who self-applied the product to gain better data on the typical consumer dose. Amendment 1 of LNX-002 made other changes in response to EPA and HSRB comments, including a revision of the discussion on how data censorship will be minimized, addition of an assay of subject attractiveness to target insects, and harmonizing changes throughout the protocol and consent form.

From September 26-30, 2009, the dose determination testing for the cream was conducted. On March 9, 2010, CLBR received a 1-year extension from IIRB because black flies are active in the spring. The field test was conducted on March 20, 2010.

The primary report was submitted to EPA in early April 2010, and EPA notified CLBR that there was no record of IIRB approval of Amendment 1. CLBR submitted a supplement including the missing document. In early June 2010, after EPA's reviews had been released to the HSRB, CLBR submitted a second supplement reporting the discovery that a second black fly species not listed in the protocol had been present in the field. In reviews, EPA considered the primary study report and both supplements, its review of the protocol, the HSRB report's review of the protocol, and CLBR supplemental submission of the IIRB roster and procedures.

EPA Science Assessment: LNX-002

Mr. Kevin Sweeney (OPP, EPA) noted that the objectives of the study were to test the black fly repellent efficacy of the test materials and to satisfy a condition of registration imposed by EPA. The test materials were a cream and a spray both containing 20 percent picaridin.

Amendment 1 added a dose-determination phase to supplement data collected in study LNX-001, and the new and old dosing data for the cream were pooled to define the standard dose rate used in this study; the dose for the spray was determined in LNX-001.

In the field study, 10 subjects were treated with each formulation and two untreated control subjects participated in the 1-day field trial in the Mojave Desert. Untreated subjects monitored black fly pressure, with two technicians attending each subject to aspirate landing flies. Treated and untreated subjects' forearms were exposed to target insects for 1 minute at 15-minute intervals, and the duration of efficacy for each subject was measured as the time from treatment to the first confirmed LIBe (FCLIBe).

Based on the mean surface area of treated arms and an assumed mean body weight of 70 kilograms (kg), the highest picaridin dose administered (cream on arms) delivered a mean dose per subject of 2.86 milligram (mg) per kg (mg/kg). The limit for picaridin dermal toxicity in the rat is greater than 2,000 mg/kg. The margin of exposure (MOE) for dermal toxicity of the picaridin cream was at least 699; mean dose for the pump spray on arms was 1.43 mg/kg with an MOE greater than or equal to 1,399. Twice as much cream was applied as spray, and as a result the dose is twice as high and the MOE is half.

Data was analyzed using the Kaplan-Meier (K-M) survival analysis, and mean complete protection times (CPT) could be calculated and were reported for both tests along with time to 25 percent failure. Field tests found the mean CPT (plus or minus standard deviation[sd]) to be 9.9 ± 2.0 hours (cream) and 9.9 ± 1.5 hours (spray); the K-M Median CPT to be 10.1 hours (cream) and 9.8 hours (spray); the time to 25 percent failure to be 9.1 hours for both cream and spray.

Regarding the role of data censorship, 5 of the 10 subjects treated with the cream experienced a FCLIBe, as did 6 of the 10 subjects treated with the spray. Censored data points

led to underestimates of the mean and sd but did not compromise K-M medians; only 3 of 9 subjects (4 from the spray group and 5 from the cream group) who did not experience failure received unconfirmed LIBes. Protocol deviations (use of a superseded data collection form, presence of black fly species *Similium tescorum*, and a 5.5-month lapse between cream dose determinations and field testing) were found to have no affect on the study.

In conclusion, the study design and conduct meet EPA guidelines and Good Laboratory Practice standards, and results are sufficiently sound to support estimates of CPT against black flies provided by the two products tested.

EPA Ethics Assessment: LNX-002

Mr. Carley stated that all the requirements of 40 Code of Federal Regulations (CFR) §26.1303 for documentation of ethical conduct were satisfied by submission of the primary study report (MRID 48053802) and the supplement showing IIRB approval of Amendment 1. None of the three protocol deviations mentioned above affected the rights or safety of the subjects or compromised informed consent.

In terms of responses to previous ethics reviews, EPA's single comment in its review of the protocol in May 2009 was satisfactorily addressed in Amendment 1. The HSRB had requested clarification of what is meant by third-party medical coverage in the consent form, which was addressed in Amendment 1 by CLBR, but not ideally. CLBR added the italicized words to the passage to clarify its promise to pay "costs of such medical treatment that are not covered by your own insurance or by a third party *that covers you*." EPA prefers: "costs of such medical treatment that are not covered by your own insurance or by *the insurance of* a third party *under which you are covered*." This change is recommended in case the insurance of a subject's family is in the name of the spouse, for example. If the Board has suggestions for better language, EPA would welcome them.

The standards applicable to this study are: 40 CFR §26.1303, requiring documentation of the ethical conduct of the research; 40 CFR §26.1703, forbidding EPA to rely on research involving intentional exposure of pregnant or nursing women or of children; 40 CFR §26.1705, the primary acceptance standard forbidding EPA to rely on data from research initiated after April 6, 2006 "unless EPA has adequate information to determine that the research was conducted in substantial compliance with subparts A through L of this part"; and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) §12(a)(2)(p), which defines as unlawful "for any person...to use any pesticide in tests on human beings unless such human beings (i) are fully informed...and (ii) freely volunteer to participate in the test. EPA's findings are that standards 40 CFR §26.1303, 40 CFR §26.1703, and FIFRA §12(a)(2)(p) were met, and notwithstanding the minor deviations noted, LNX-002 was conducted in substantial compliance with all applicable requirements of 40 CFR part 26, subparts K and L. In conclusion, if LNX-002 is determined to be scientifically acceptable, there is no barrier in law or regulation to impede EPA's reliance on it in conducting actions under FIFRA.

Board Questions of Clarification

Dr. Vanessa Northington Gamble noted that one objective of the study was to satisfy a condition of registration, and asked what was meant by the term and what EPA would do with the completed study. Mr. Jordan responded that the pesticide law requires EPA to approve every pesticide product before sale, and the process for pre-market approval is called registration. When a product is presented to EPA, the Agency may allow it into the market with conditions that the company must satisfy to keep the product on the market (conditions of registration). This study was a condition of registration for the picaridin products in order to confirm language on efficacy used in labeling. The product is on the market, and now has satisfied conditions of registration and can remain on the market.

Dr. Dallas Johnson asked EPA to address the change in the protocol to 1 minute of exposure in 15-minute intervals instead from 5 minutes of exposure in 30-minute intervals. Mr. Carley replied that in EPA's protocol review, Mr. Sweeney called for a change because the Agency was accustomed to seeing protocols from CLBR using exposures of 1 minute in every 15; EPA has accepted and will accept both designs in the future, but the choice of 5 minutes in 30 was not adequately explained.

Dr. Sidney Green, Jr., observed that the HSRB had made a number of recommendations to approve the protocol in June 2009, but in the summary presented they were not mentioned. Mr. Carley explained that HSRB recommendations included focusing the test on black flies (which was addressed in the amendment) and changing the consent form on third-party medical insurers. In EPA's view, EPA and HSRB comments were addressed. Dr. Green added that other science recommendations from the HSRB, such as one on CPT, were not mentioned. Mr. Carley noted that the Agency's policy conclusion, taking into account HSRB advice, is that tests of CPT are the most appropriate study design to support claims on pesticide labeling. In some other contexts, other study designs are more credible. Dr. Green added that the HSRB made a number of recommendations that did not appear in Mr. Carley's study summary, but that were addressed by CLBR in the protocol modification. Dr. Philpott suggested that EPA should be more explicit in a point-by-point review of the HSRB recommendations of completed studies.

Dr. Sharpe requested some context for a point in the proposal on page 23: "Despite the comparatively long duration of exposure after application in the study, only 5 of the 10 subjects testing cream and 6 of the 10 subjects testing spray reported failures." She asked what constituted a failure. Mr. Sweeney responded that a failure occurred when a subject experienced a black fly landing, then a second landing. From a statistical viewpoint, it would be beneficial if every subject failed so that a more accurate CPT could be calculated, but the study was run for an entire day. Mr. Carley added that failure means a failure of complete protection defined as a confirmed LIBe, which is a pest landing confirmed within 30 minutes by another landing. Not only is EPA concerned about the distribution of results from the perspective of the subjects, but also about the distribution of the black fly behavior. The Agency is attempting to approximate typical behavior of the pest insects, as well as the distribution of results by subject.

Dr. William Popendorf asked whether the resulting data from the dosimetry test were significantly different that LNX-001. Mr. Sweeney responded that the dose was lower; it was

initially estimated as more than 3 mg, and the new result was 2.36 mg. Mr. Carley added that the new dose result fell halfway between the LNX-001 result and the cream tested by the other laboratory. Dr. Popendorf noted that the result did not seem significantly different. Dr. Philpott suggested that Dr. Scott Carroll, CLBR, may be able to provide more clarification. He expressed interest in the fact that the earliest failures seemed to be on subjects who applied less product. Mr. Carley stated that in the repellent stage, all subjects received the same dose. Dr. Philpott expressed curiosity about whether there were studies that relied on consumer application doses. Mr. Carley added that he was not aware of a repellency trial in which the dose was not controlled.

Dr. Linda Young commented that as repellents with extended protection time are tested, the endpoint in trials should be examined, as it presents a problem if half the subjects are censored. If half do not have failures, alternative measures should be considered.

Dr. Fernandez noted that most field trials in agriculture were conducted in multiple sites, and asked if it was common and acceptable practice in pesticide research to conduct a field study in one location. Mr. Sweeney replied that there have been studies with one site and those with multiple sites, but sites with sufficient biting pressure from black flies are not as abundant as mosquito sites. In addition, other flies have been tested for this product, so there is a fairly strong data set. Mr. Carley noted that field studies with mosquitoes have to be conducted in two different habitats where the species distribution is different. The typical requirement for black flies is for one habitat or field location. Dr. Young added that the species varies widely across the United States, and this needs to be considered because almost all the studies seen are conducted in California.

Dr. Gamble referenced the presence of a different species than had been anticipated and asked if it made a difference in the study. Mr. Sweeney noted that it did not appear to make a difference; landings were experienced from both species.

Dr. Chambers inquired if there were sufficient data on black flies from laboratory studies that confirm the field study results. Mr. Sweeney responded that other black fly field studies were found in the literature. Dr. Chambers asked whether any laboratory studies complement these field studies. Mr. Sweeney replied that there were laboratory studies on stable files but not on black flies.

Dr. Gamble asked what was meant by the phrase "substantial compliance" used in the ethics review. Mr. Carley explained that this was a question raised by petitioners when they challenged the rule. Mr. Jordan will be discussing the subject during his presentation on the settlement during the afternoon session.

At this point, Dr. Carroll, Principal Investigator, and Mr. Shawn King, Director of Operations, CLBR, joined the meeting to field Board questions.

Dr. Popendorf questioned if the number of landings on the untreated controls experienced in one minute had been recorded. Dr. Carroll responded that exposure was ceased after the first landing was observed; there may have been cases of two simultaneous landings, but only a single

landing was recorded. Dr. Popendorf asked if the time of landing had been recorded, and Dr. Carroll replied that it had not been recorded specifically within one minute. Dr. Popendorf further asked whether the time of landing could be recorded to gain a better understanding of the biting pressure in future protocols. Dr. Carroll agreed that this could be conducted, and that these data on the temporal distribution of actual landings would be interesting.

Dr. Sharpe asked how the particular institutional review board (IRB) was chosen. Dr. Carroll answered that the choice of IIRB was based on consultation with the California Environmental Protection Agency. CLBR conducts its tests principally in California, because many sponsors want the tests conducted there as California is prone to require more tests than many other states. CDPR personnel mentioned that IIRB was paying closer attention than most to the developing federal rule governing human exposure studies at EPA. Dr. Sharpe commented that she was unsure how many IRBs would be available to conduct a review of a study such as this, and it is interesting that the chosen IRB had particular expertise.

Dr. Prentice asked if IIRB is accredited by the Association for the Accreditation of Human Research Protection Programs. Dr. Carroll responded that he believed that it was accredited, but had not examined its paperwork. Dr. Prentice added that this was an important criterion for IRBs, and asked how subjects traveled from the CLBR laboratory to the field site. Dr. Carroll responded that in this case, the subjects drove rental vehicles, but more commonly subjects drive their own vehicles. Dr. Prentice inquired if a subject were in an accident driving to the site, if he or she would be covered by CLBR's insurance, because compensation is mentioned for those subjects "injured as a result of participating in this study." Dr. Carroll noted that he had asked this question of the insurers and attorneys, and did not receive a clear answer. When rental vehicles are used, additional insurance is purchased so that the drivers are covered. The attorneys with whom he consulted recommend always extending CLBR's responsibility to the maximum reasonable level.

Dr. Gamble questioned if there are many studies in which subjects have to travel several hours to a field site. Dr. Carroll responded that all field studies require some travel, and usually a minimum of 1.5 hours.

Dr. Popendorf asked about the mean values in the exposure test, and whether the second group of people in the dosimetry test was significantly different from the first, or if the change in the mean rate was nonsignificant. Dr. Carroll noted that the intention was to pool the values as being from the same population. The variance was very high in the first pool of 10 people, with a dosage rate range of approximately 10-fold principally attributable to a single extremely heavy applicator. The range in the second group of 15 was smaller, and the dosing rate was reduced by approximately 20 percent overall.

Public Comments

Dr. Carroll, CLBR

Dr. Carroll noted that CLBR finds itself in an interesting position as practicing scientists, which is midway between the HSRB's purview and EPA's historical and newly revised guidelines and the needs of industry. The greatest challenge is to provide effective, adequate samples that give good guidance, which uses relatively few subjects testing in relatively few places; CLBR works very carefully to maximize the information quality. CLBR, for example, has worked at field sites with up to 10 species of mosquitoes, which are rare. The people from industry who request these studies are conscientious, but do not want to do more than the Agency requires. Still, they have allowed CLBR to increase sample size to levels with which it is comfortable. A strong history exists in this field of the production and sale of successful insect repellents that have served U.S. and international consumers well for decades based on guidelines of this nature. To this point, aspects of the biology of biting insects and the repellents that have been released combine to offer relatively reasonable pictures based upon studies such as this.

Dr. Philpott called for additional public comments, and none were received.

Charge Questions

Mr. Carley read into the record the two charge questions:

- Is the CLBR study LNX-002 sufficiently sound, from a scientific perspective, to be used to estimate the duration of complete protection against black flies provided by the tested repellents?
- Does available information support a determination that study LNX-002 was conducted in substantial compliance with subparts K and L of 40 CFR part 26?

Board Science Review: LNX-002

Dr. Green opened the Board's science review of protocol LNX-002 by noting that on May 18, 2009, EPA reviewed the CLBR protocol and determined it did not address two elements: the justification for biting pressure, and the justification for sampling once for 5 minutes every 30 minutes instead of for 1 minute every 15 minutes. In June 2009, the HSRB concurred with the recommendations of EPA's science review, but also made additional recommendations. Board recommendations concerned the particular species on which data would be collected and the calculation of CPT. The Board recommended that the study be conducted on black flies or biting midges only. CLBR modified the protocol accordingly on page 166. The Board also recommended that the protocol be amended to explain better how mean CPT would be calculated accurately using statistical analyses; CLBR complied by modifying the protocol on page 190. Additionally, the Board recommended that the study duration should be sufficiently long to ensure that the repellent will fail for a substantial portion of study participants, and CLBR amended the protocol on page 187. Finally, the HSRB recommended that the protocol be revised to clarify how the analysis will proceed in the presence of

censored data, and CLBR modified the protocol on page 191 to account for Board comments. On August 13, 2009, CLBR amended the protocol to address HSRB and EPA comments. In May 2010, EPA conducted another science review of the protocol and determined that the study was scientifically sound and acceptable. In Dr. Green's review of the amended protocol, he noted that the recommendations were followed as stipulated, and the protocol is scientifically sound and acceptable, agreeing with the EPA's science review of the protocol.

Dr. Chambers concurred, noting that the two deviations mentioned did not affect the scientific outcome. Dr. Johnson also agreed with the science review.

Dr. Popendorf noted that the data allow the calculation of the effectiveness of the repellent during that time, and suggested that future studies include that calculation. It would add a valuable dimension to future studies of this nature.

Dr. Chambers suggested that when the HSRB has future recommendations, that the reports list them in a separate category so it does not seem that they apply to the particular studies that were reviewed. Dr. Philpott stated that the Agency and sponsors understand that these are future recommendations, and agreed that they could be listed in a separate section in the report. Board members must keep in mind that the HSRB is an advisory body, and while EPA and sponsors appreciate the recommendations, they are not required to incorporate them.

Dr. Michael Lebowitz recommended that if there have been laboratory studies on the same or similar species, it would be interesting to have some note of that in the EPA review, because it would allow for consideration of similarities or differences that might be scientifically justified and useful in a broader sense. It would be helpful because it is difficult for members not in that specific field to get this information, and it may help the HSRB to reach conclusions.

Dr. Philpott suggested that the Board make a consensus recommendation that the answer to the first charge question is yes, CLBR study LNX-002 is sufficiently sound, from a scientific perspective, to be used to estimate the duration of complete protection against black flies provided by the tested repellents. The Board has some additional future recommendations for the Agency and the sponsors. Dr. Popendorf recommended that if the data are robust enough to determine the effectiveness of the repellent over time, that calculation be included in the analysis; Dr. Lebowitz suggested that EPA include any related laboratory studies on the same or similar species in its scientific review.

Board Ethics Review: LNX-002

Dr. Gamble noted that as Mr. Carley discussed, the protocol was submitted to the Board for review in June 2009, and in its report of October 2009, the HSRB concluded that with modifications, it was likely to meet applicable requirements. The sponsor has responded to recommendations, especially in terms of the third-party language. She reviewed the entire protocol and did not determine any ethical issues. The Board needs to decide if EPA's recommended language on the third party should be used or if changes are needed because the issue was raised with another protocol as well. She stated that the study is in substantial compliance with 40 CFR part 26, subparts K and L.

Dr. Philpott added that perhaps the Board can recommend some language to consider with respect to a third party.

Dr. Prentice mentioned that substantial compliance was discussed in other meetings, and that he did not care for the term. He agrees that the study was in compliance with 40 CFR part 26, subparts K and L but does not understand what "substantial" means in this case. Either a study is in compliance or not, and that judgment must be made. He raised concerns about compensation in case of injury, and agreed with Dr. Gamble that the Board ought to discuss whether it concurs with EPA's recommendation for the rewording of the insurance clause. He suggested further clarification of the relationship of the injury to the study; it should state injury "as a direct result of being in the study." This change will help to avoid confusion if there should be an injury. Dr. Prentice commented that the system of conducting reviews is interesting. EPA reviews the protocol and makes comments based on competent science and ethics considerations. The HSRB reviews the protocol, makes recommendations, then reviews it again when the study is complete. If EPA and the HSRB have done their jobs, and research is conducted in accordance with the way it was approved, the Board should have nothing to discuss except for future recommendations. The Board may be able to identify areas that should be improved. He noted, however, that the Board was unsure which recommendations had been incorporated, and it is important that this be clearly indicated. If a recommendation from the HSRB is not accepted, the Board should know why. In this case, all the recommendations were accepted, and the study was conducted in substantial compliance with 40 CFR part 26, subparts K and L.

Dr. Philpott asked Mr. Jordan whether "substantial compliance" was the language used in the regulation. Mr. Jordan responded that it was. Dr. Philpott noted that the question may need to be discussed more broadly in the future, but that the Board needed to decide what criteria it is using to define substantial compliance, because it is true that a study is either in compliance or not. Dr. Prentice agreed that the Board's interpretation of the term has to be determined. The word "substantial" should not result in the Board compromising its reviews. Dr. Gamble added that when the topic was discussed in June 2009, the criteria of acceptable risk-benefit ratio, voluntary and informed consent of all participants and equitable selection of the study participants were used. Whether the Board wants to use those criteria or additional ones needs to be discussed. Dr. Philpott stated that this is a recommendation to the Board, not to the Agency or the sponsors, to be explicit in language, definitions, and criteria that are used. This may be an item that needs to be placed on the agenda for the next Board meeting.

Dr. Prentice stated that the HSRB had to determine whether the study was acceptable or not, and if it is unacceptable, the study should not be conducted. Dr. Jerry Menikoff observed that the regulations are complicated, and in almost any study there is some degree of noncompliance with their many provisions. Often that noncompliance is trivial and does not affect the subjects.

Substantial compliance is mentioned in the regulations, and the Board could interpret it to mean that a study is not in substantial compliance if the noncompliance alters the protection of subjects. The HSRB should not recommend that the word "substantial" be removed because it offers flexibility. The Board, however, must be careful to ensure that it is not being used to diminish protections for subjects. Dr. Philpott commented that Dr. Prentice did not intend to

recommend that substantial be removed from the regulations, but to recommend that the Board define how it views compliance and noncompliance. Dr. Prentice asked if in review of a protocol that has not been initiated, the Board is applying the term "substantial compliance." Mr. Carley responded that "substantial compliance" only occurs in the rule in the section stating that EPA cannot rely on the results of a study not conducted in substantial compliance with the standards. There is no comparable regulatory standard for protocol review: the regulations state only that EPA and the HSRB must review the protocol, and it would be considered "reviewed favorably" or not. Dr. Prentice suggested that when the Board initially reviews a protocol, it should be determined whether it is in compliance if conducted in accordance with the regulations. It is true that minor noncompliance occurs in studies; that does not mean that human subject protections are compromised. If there were deviations from the protocol when the study was conducted, any effect on the data and the ethics should be determined.

Mr. Jordan explained that the 2006 version of the rule that includes the phrase "substantial compliance" has been the subject of ongoing controversy. One of the questions that arose when the rule was proposed asked what EPA meant by "substantial compliance," "fundamentally unethical," and "significantly deficient." He read from the answer that EPA offered when promulgating the final rule, which follows Dr. Menikoff's thinking: "In recent years EPA has reviewed numerous reports of completed research on pesticides involving intentional exposure of human subjects. Case studies have been conducted over many years in many places under a variety of ethical policies and regulatory schemes. They have addressed a wide range of research questions and presented a wide spectrum of ethical shortcomings from minor flaws to more serious deficiencies. Given these variations, the Agency believes that its ethical framework must retain sufficient flexibility to judge each situation on its merits in the context of the time and place." The section continues with a discussion of existing documents such as the Nuremberg Code, the Belmont Report, and the Common Rule and how those might guide the decision-making. EPA will rely on these when they are appropriate for the evaluation of a particular study, but the gravity of a particular ethical lapse depends on the details of the deficiency and the circumstances under which it occurred. EPA agrees with the National Academy of Sciences (NAS) that each study requires case-by-case evaluation and EPA expects the terms mentioned to gain greater clarity over time through HSRB and public review of Agency decisions concerning reliance on completed studies. The question about "substantial" also arose in the HSRB's early discussions, and EPA noted the language that was just read. Based on that discussion, the Board determined its own understanding of what "substantial" meant: a proposal would be found unacceptable if the amendments to or deviations from the proposal placed participants at increased risk of harm based on knowledge available at the time the study was conducted or impaired their informed consent. Dr. Prentice asked if the Board determined that a study was not in substantial compliance, what EPA would do with the recommendation. Mr. Jordan responded that this situation has occurred; agreement with EPA's reviews varied, but in every case EPA found the Board's reasoning to be persuasive and did not rely on the studies that the HSRB found not to be in compliance.

Dr. Philpott commented that the Board had been discussing the evolution of its thinking and reexamination of the criteria used. This topic may be raised again in the afternoon's discussion of the lawsuit settlement. Dr. Gamble noted that the third-party language needed to be clarified to offer EPA some guidance on what it should say. Dr. Philpott noted that the language

was probably in the study LNX-003 as well, so the Board can return to it during the ethics discussion for that study.

Dr. Philpott stated that the Board's consensus answer to the second charge question is yes, but that there are recommendations that go beyond the review of this protocol with respect to the language on the third party. He noted that Dr. Prentice recommended that for future protocols, the relationship of an injury to the study participant be clarified, and that the phrase "direct result" be used.

Completed CLBR Study LNX-003: Laboratory Repellency of Two Picaridin-Based Personal Insect Repellents to Two Species of Ticks

Background

Mr. Carley noted that LNX-003 was conducted in the laboratory because robust field tests for tick repellency are not available. The study tested the repellency of two picaridin-based repellents against laboratory-reared, pathogen-free ticks of two species. Subjects were trained to handle ticks before the study, which involved 20 subjects (10 with each repellant) treated on one arm with the standard dose rates as determined in LNX-001 and LNX-002. The untreated arm of each subject was used to confirm tick aggressiveness and subject attractiveness to the species.

Each subject was prepared the same way on both arms, with a boundary line drawn at the wrist that would be the edge of the treated area on the treated arm. A parallel line was drawn 3 centimeters (cm) toward the elbow (the crossing line), and a point was drawn 3 cm down the hand (the starting point). Each tick was placed at the starting point on the subject's untreated arm with a paintbrush or similar implement, and the tick was oriented toward the wrist. The subject placed his/her fingers on the table with the elbow raised, and if the tick moved up the arm across the crossing line, it qualified as an actively questing tick to be used in the repellency trial. The qualified tick then was placed at the starting point on the treated arm, and the species behavior was observed for 3 minutes. It was counted as a crossing if the tick traveled across the crossing line; if not, it was counted as repelled.

The study was designed in a sequence of exposure cycles that lasted 15 minutes, in which time a tick of each species was tested. The endpoint was the first confirmed crossing for each tick species for each subject; the confirming crossing was a second crossing by the same species within 30 minutes. The cycle was repeated 60 times over 15 hours. All of the ticks qualified in the first test.

The protocol dated July 26, 2009, was approved by IIRB with a minor correction on August 4, 2009, and was submitted to EPA on August 6, 2009. The protocol met the standard of completeness defined in 40 CFR §26.1125. The science and ethics reviews were conducted in September 2009 based on the initial protocol submissions, and were sent to CLBR. The HSRB reviewed the protocol favorably in October 2009.

Amendment 1 was made on October 30, 2009, to respond to EPA, HSRB, and CDPR comments. The amendment clarified which procedures apply to one, both, or either tick species;

how subjects would be screened for attractiveness to ticks; and stopping rules. It also corrected minor errors and confusing statements and made harmonizing changes to the consent form. A version of the protocol with tracked changes, some dated previous to EPA and HSRB reviews, is included in meeting materials with the primary study report: these changes were incorporated into Amendment 1. The amendment was submitted to IIRB on November 2, 2009, and approved on the same date after an undocumented expedited review. The amended protocol was approved by CDPR on November 16, 2009. The investigators complied fully with all requirements in interactions with the IRB; they asked the IRB to send them the minutes from the meeting at which Amendment 1 was approved, but there were no minutes available due to the expedited review. The correspondence on this topic is included in the primary report. Mr. Carley reviewed IIRB's procedures and also asked for records of the meeting; IIRB responded that no records existed. Mr. Carley referred this response to Dr. Warren Lux, EPA's Human Subjects Research Review Officer, and asked him to consider whether a response from EPA to the IRB would be appropriate. Mr. Carley reiterated that any concerns that EPA has about the review process do not reflect on CLBR.

In early January 2010, CLBR received the ticks for the subject training session from the Centers for Disease Control and Prevention (CDC). The training session was conducted in mid-January, repellency ticks were received from CDC on January 20, 2010, and the repellency testing was conducted January 23 and 24, 2010. The report on the study was completed and submitted in April 2010.

EPA Science Assessment: LNX-003

Mr. Sweeney noted that the objectives of the study were to test the repellent efficacy of two test materials against nymphal ticks of two species. The test materials are the same as in LNX-002; a cream and spray each containing 20 percent picaridin.

Twenty subjects and three alternates were trained in the laboratory to handle ticks and to remove them before they could bury and bite. Ten subjects were treated with each test material, and were tested on each of two successive days. The untreated arm of each subject was used to test that ticks were questing actively, and each subject was tested on a nymphal tick of each species in each 15-minute exposure period until failure or approximately 15 hours post treatment. CPT was calculated for each subject as the time from treatment to the first confirmed crossing.

The amount of repellent applied was slightly different from the previous study; mean applied was 0.52 grams (g) (spray) and 0.96 g (cream). Mean picaridin applied was 104 mg (spray) and 192 mg (cream). A MOE of 100 is a level of concern, and the MOEs were very high in this study: 1,342 (spray) and 730 (cream).

A K-M median could be calculated for the spray, but the data for the cream were too heavily right censored to support calculation of the median. Mean CPT values and time to 25 percent failure were reported for both products. For *Ixodes scapularis,* the mean CPT ± sd was 12.6 ± 4.3 hours and time to 25 percent failure was greater than 15.4 hours for the cream, and for the spray were 14.1 ± 11.8 hours and 13.1 hours, respectively, with a K-M median CPT of 15.0 hours. For *Dermacentor variabilis*, the mean CPT ± sd was 15.3 ± 0.3 hours and time to

25 percent failure was 9.7 hours for the cream, and for the spray were 14.0 ± 1.6 hours and 12.0 hours, respectively, with a K-M median CPT of 14.1 hours. For the spray, 5 subjects experienced a confirmed crossing with ticks of each species, and for the cream 2 subjects experienced a confirmed crossing for *Dermacentor variabilis* and 4 subjects experienced a confirmed crossing for *Ixodes scapularis*.

EPA found that the study design and conduct meet EPA guideline and Good Laboratory Practice standards, and study results are sufficiently sound to support estimates of the CPT provided against both tick species by the two products.

EPA Ethics Assessment: LNX-003

Mr. Carley stated that the ethics assessment considered the primary study report, EPA science and ethics review of the protocol, the HSRB report on the protocol, the IIRB roster and procedures, and the EPA-IIRB e-mail exchange dated April 20, 2010. The requirements of 40 CFR §26.1303 to document ethical conduct of the research were satisfied.

In EPA's review of the LNX-003 protocol, it asked CLBR to reclassify two exclusion criteria as stopping rules (addressed in Amendment 1) and to revise the statement in the consent form concerning payment for uninsured medical expenses. The latter recommendation was not addressed fully; CLBR used the same language as in LNX-002. The preferred language remains in a transition phase until EPA hears the Board's opinion on the topic. Mr. Carley agrees with the comment that when a proposal undergoes EPA, HSRB, IRB, and CDPR review, and is approved and executed according to the protocol, not much discussion is required after it is conducted. In this case, CLBR wrote a good protocol, executed it as planned, and made changes in the protocol to address the comments made by reviewers.

The same standards apply to this protocol as to LNX-002: 40 CFR §26.1303, requiring documentation of the ethical conduct of the research; 40 CFR §26.1703, forbidding EPA to rely on research involving intentional exposure of pregnant or nursing women or of children; 40 CFR §26.1705, the primary acceptance standard forbidding EPA to rely on data from research initiated after April 6, 2006 "unless EPA has adequate information to determine that the research was conducted in substantial compliance with subparts A through L of this part"; and FIFRA §12(a)(2)(p), which defines as unlawful "for any person...to use any pesticide in tests on human beings unless such human beings (i) are fully informed...and (ii) freely volunteer to participate in the test." EPA's findings are that standards 40 CFR §26.1303, 40 CFR §26.1703, and FIFRA §12(a)(2)(p) were met, and notwithstanding the failure to revise the consent form language as directed by EPA, LNX-003 was conducted in substantial compliance with all applicable requirements of 40 CFR part 26, subparts A to L.

In conclusion, assuming LNX-003 is determined to be scientifically acceptable, EPA finds no barrier in law or regulation to EPA's reliance on it in actions under FIFRA.

Board Questions of Clarification

Dr. Popendorf asked if both species were tested in 15 minutes. Mr. Carley responded that within each 15-minute period, all steps in slide 5 of EPA's LNX-003 presentation are completed (ticks of both species are tested for questing and then repellency is tested). There is barely time to conduct all these steps in 15 minutes, but the ticks were very active, and all qualified for the test. EPA questioned the timing during the protocol review, but Dr. Carroll reminded the staff that a study using two species in 15 minute cycles had been conducted before, and during this study, no reporting periods were missed.

Dr. Menikoff commented that EPA noted that the failure to implement the wording change in the consent form was a minor deficiency. He asked if the Agency was suggesting that this failure meant that there was not full compliance with the regulations. Dr. Philpott clarified that there are always deviations, but as long as they are not severe enough to impact subjects, they are not substantial. Dr. Menikoff noted that it was not obvious to him that there was any deviation; it is unclear how the failure to correct that sentence means that there is in any way noncompliance with the regulations. Mr. Carley responded that EPA does not believe that the failure of the investigators to adopt the exact language in the review constitutes noncompliance in any respect. Under 2006 regulations, neither EPA nor the HSRB can approve a protocol; a protocol is reviewed and recommendations are made, and consistent with NAS's recommendation, it is considered that the investigator might have knowledge that the reviewers lacked that would justify taking action other than that recommended. Investigators also knew that the study would be reviewed by the Board again, and any investigator who ignored recommendations risked that the resulting study would not be considered in EPA decisions. Because there is not a formal regulatory approval for the protocol, the failure to respond verbatim to recommendations does not constitute noncompliance with the rules. Dr. Philpott suggested that the Board return to the topic in the discussion period.

Dr. Sharpe mentioned that the consent form states that the cream repellent will cause substantial but temporary injury to the eyes on contact, and that subjects can obtain more information about the safety of repellents by asking a technician. She asked why this statement is sufficient for disclosure of risks. Mr. Carley replied that the language in question is taken from the label. In this particular case, investigators apply the product to one forearm and observe the subjects throughout the study. The risk discussion in the protocol states that the likelihood of eye contact in these circumstances is negligible. EPA was comfortable with that aspect of the consent form. Dr. Sharpe suggested that information on a label is for consumers and information on an informed consent form is for subjects; they may not be analogous. Dr. Philpott noted that this point should be considered in future protocol reviews.

At this point, Dr. Carroll and Mr. King joined the Board to field members' questions.

Dr. Popendorf asked about the manipulation of the ticks to encourage them to move in the right direction and its effect on the study results. Dr. Carroll responded that manipulation is based on experience from handling ticks. Both species used in the study are active, and there seems to be a constant velocity at which they move. They tend to move from distal to proximal regardless of the arm position. The CDC ticks were not as inclined to move in a set direction as

some Dr. Carroll had used previously. Movement in the wrong direction confounds what CLBR is trying to test. The ticks are not difficult to manipulate, and tend to follow the trajectory they have attained once manipulation ceases. Their behavior changes abruptly when encountering repellent; they stop, or start to explore the margin, and the impact of the manipulations on their trajectory seems very small in comparison. There are a maximum of four attempts, or no more than 1 minute of manipulation.

Dr. Popendorf asked if the ticks were placed on the back or front of the arm. Dr. Carroll responded that they were placed on the front of the arm where they move faster because not as much hair is present.

Dr. Sharpe asked whether perfume, alcohol, and cigarettes were exclusion criteria, and if any studies were conducted that did not have these excluded, but tested the repellent in real-life conditions. Dr. Carroll stated that the approach taken was based on the tradition of repellent testing in which obvious confounding factors are minimized.

Public Comments

Dr. Philpott called for public comments and none were received.

Charge Questions

Mr. Carley read the charge questions for the study into the record.

- Is the CLBR study LNX-003 sufficiently sound, from a scientific perspective, to be used to estimate the duration of complete protection against ticks provided by the tested repellents?
- Does available information support a determination that study LNX-003 was conducted in substantial compliance with subparts K and L 40 CFR part 26?

Board Science Review: LNX-003

Dr. Popendorf noted that the protocols were reviewed and the study was conducted in compliance with the protocol. The answer to the first charge question is yes, the study provides sufficiently sound scientific data for the duration of complete protection against ticks.
Dr. Lebowitz stated that he agreed.

Dr. Fernandez prepared a presentation not specific to the particular study. He expressed concern about the sample size used in the study, and conducted some power analysis to see if it was large enough. He analyzed sample sizes of 5 and 10 and found the computed power to be 0.25. This should be considered for future studies. Dr. Fernandez noted that the median survival time and time to 25 percent failure were reported without a confidence interval (CI). He determined the CI's lower boundary to be 3.4 for the cream tested on the *Ixodes scapularis* species, and suggested that the CI be included in study reports.

Dr. Philpott asked if Dr. Fernandez found the data in the study to be scientifically valid. Dr. Fernandez responded that he had no objections to the data.

Mr. Carley asked, considering that the CI corresponded to the data range, whether anything new was learned from the CI. Dr. Young responded that the CI measured how well the data results had been calculated. The lower bound of the CI needs to be used as the estimate in the interest of public safety; there is then 95 percent certainty that the median is at least that large. When that figure is used, the results look less impressive.

Dr. Philpott asked whether Drs. Fernandez and Young believed the data are scientifically valid and could be useful for decision-making purposes, but a recommendation is being made to the Agency about how to interpret the data. Dr. Young responded that this topic applies to the discussion of the revised guidelines.

Dr. Popendorf noted that the gray area (CI) matches the data range and asked if this was the result of having sample size of 10. Dr. Fernandez responded that this was likely to happen whenever there was a small sample size.

Dr. Philpott stated that the consensus agreement from the Board on the first charge question is yes, the CLBR study LNX-003 is sufficiently sound, from a scientific perspective, to be used to estimate the duration of complete protection against ticks provided by the tested repellents. The HSRB needs to note the caveats from Drs. Fernandez and Young and will explore them further in discussion of the new guidelines.

Board Ethics Review: LNX-003

Dr. Menikoff noted that he agreed with Mr. Carley's analysis and came to the conclusion that the study appears to be in substantial compliance with 40 CFR part 26, subparts K and L. It is not obvious from what the Board has heard on the study that there is any degree of noncompliance with the subparts.

Dr. Sharpe did not have any further comments.

Dr. Philpott noted that the consensus recommendation from the Board on the second charge question is yes, the available information supports a determination that study LNX-003 was conducted in substantial compliance with 40 CFR part 26, subparts K and L.

OPP Presentation: Revised Product Performance Test Guidelines for Insect Repellents to be Applied to Human Skin

Mr. Jordan commented that as a consequence of the Human Studies Regulation, EPA and the Board have spent much more time reviewing protocols for insect repellents than they had before 2006, and as a result of the reviews there has been a great deal of productive conversation. The Board has provided EPA and the investigators with valuable advice; there have been significant improvements in studies since 2006. EPA has tried to capture the state of the art in the

guidelines. When discussing the science of the testing, how the data will be used and how they relate to the regulatory framework also must be considered. Some of the discussions have challenged EPA to examine what was done in the past and what should be recommended in the future.

EPA considered comments from the Board on previous drafts of the guidelines, and tried to capture the ideas. EPA considered three important policy issues when revising the guidelines: the objective of repellent efficacy testing, the choice of endpoint for repellent efficacy studies, and statistics and handling of censored data. Two overarching policy factors also have played a role in how the guidelines were constructed. Consistency of approach is always beneficial, perhaps even a legal requirement. If two products are similar, they should face the same regulatory requirements. Additionally, if the regulatory requirements are going to change, EPA should consider how they can be implemented in a fair and efficient manner and what that would mean in terms of burden on EPA and the regulated community.

At the outset, EPA faced a basic choice: whether to stay with a testing approach that is similar to what companies have been using in the past, or to move to something that is significantly different. The historical approach has limitations. In field studies, variable conditions, such as weather and pest pressures, can affect the apparent efficacy of repellent products. In some cases, the same repellents tested at different times in the same location with the same subjects resulted in different answers about the level of protection. EPA has considered moving toward tests with mosquitoes in laboratories so that conditions could be controlled better. The Agency decided not to take that action, and will continue to accept data from laboratory studies, but will encourage investigators to conduct field studies. Repellents in field conditions do not always perform as well as in the laboratories. The Agency also considered requiring more test sites or larger sample sizes, which would improve the reliability of the results, but cost is a consideration. EPA decided that improvement in quality of data will not justify the added cost, and the basic approach will remain the same. Currently, approximately 150 different insect repellents are registered, and efficacy testing has been conducted for almost all of the products. Most previous studies have used the same basic approach and tested for the complete duration of protection. The studies have been the basis for labeling claims on the products, and adopting a radically different approach would mean having to retest most of the products. If a new approach were taken for new products, it would mean that labeling on new products would be different from those already on the market, and two products stating 9 hours of CPT, for example, could have differences in real efficacy. Therefore, EPA believes that it makes the most sense to use the same basic approach as in the past.

The testing objective is to measure the duration of complete protection. EPA's own research and market research by the companies who sell the products determined that consumers expect complete protection from repellents.

The preferred study endpoint is the first confirmed failure event, which is an event that indicates that the repellent is no longer successfully repelling the insects. The specific failure event depends on the behavior of the particular pest. A confirmed failure is an event (first confirmed event) followed within 30 minutes by another event (the confirming event). Using a confirming event as the endpoint means that the test subjects will experience more bites and

landings than they would if the first unconfirmed failure event were chosen, which has implications for subject safety and appearance of how long the repellent is providing protection. These considerations are outweighed by the use of confirmed failure, because it reduces the variability in the results.

The preferred summary statistic is the K-M median CPT with a 95 percent CI. The median value will be taken as the representation of CPT for the trial, and that value will be used in determining what labeling claims are acceptable for the tested repellents. The CPT endpoint in labeling language is a matter that will be handled outside the guidelines through a standard evaluation procedure, which is still in the drafting stage. Investigators will be encouraged to design studies in a way that reduces the likelihood of censored data, but that may not always be possible as products with longer CPT are developed and tested. In addition, there are practical limitations on how long a test subject can be asked to participate in research to evaluate repellent efficacy. In circumstances where censored data are present, they will have to be used to characterize CPT. Censored data points will be treated as a confirmed failure event to calculate median or mean value, hence the calculation of a mean CPT in the face of right-censored data will be an underestimate of the mean CPT, and the variability of the data will be underestimated. From a policy perspective, this type of error is acceptable in that it will not mislead consumers to expect a longer period of efficacy than applies. EPA still is open to hearing the HSRB's ideas on how to examine and analyze the data. As long as repellency data is reported fully for the individual subjects, EPA can decide to change the way it is analyzed.

The new guidelines reflect these policy positions, and are not binding, but represent EPA's recommendations to investigators and expectations that in general, if the guidelines are followed, a company's data will satisfy EPA's regulatory requirement. It is always possible for a company to suggest something about the study that ought to change and discuss this with EPA. If a study involves potential exposures, EPA will review it and bring it to the Board.

Mr. Carley noted that this is the third generation of revised guidelines. The guideline currently in use dates from 1999, and was released as a draft guideline for use. After it was issued, there was a review by the FIFRA Scientific Advisory Panel, which issued a significant range of comments, and public comments were submitted as well. Since the Human Studies Rule was promulgated, all new repellent efficacy studies have come through the Board as proposals before they were implemented. None of them have corresponded only to the minimum standards of the 1999 rule, which states that sample size has to be six; the Board has not reviewed a proposal with a sample size less than 10. There have been issues about whether the rationale for the sample size was compelling, but the Board has not yet taken exception to the proposed sample size or to the acceptability of the sample size of the completed studies. Before EPA brought the first proposal for a repellent study to the Board, it brought the HSRB a revision to the 1999 guideline that reflected what had been learned during the previous years and considered the Human Studies Rule. EPA received helpful comments from the Board and accumulated HSRB comments on the studies reviewed to produce a substantial revision that the Board reviewed in 2008. The current revision is less significant in scope, and was more of a refinement, but it has been 11 years since the previous guideline was released, and an updated guideline needs to be issued as soon as possible.

Data requirements are not defined by the guidelines but by regulations. These regulatory data requirements are stated in general terms that must be interpreted and applied on a case-by-case basis. The general regulatory requirement for data to support labeling claims was interpreted and applied by Mr. Sweeney and his colleagues in the Registration Division to require the studies reviewed at this meeting. When the data requirement has been interpreted and applied to a particular case, the guidelines apply. The guidelines recommend to sponsors and investigators appropriate methods for testing to address a particular requirement. They do not have the force of regulations and the methods they describe are not mandatory. Deviating from the recommendations is not an issue of noncompliance; investigators are free to propose and justify other approaches, and EPA can accept other approaches. In this draft, the word "must" is used only when EPA was quoting or summarizing a requirement that is established in regulation. The word "should" is used in all other situations.

After investigators have conducted a study, EPA staff review the report under internal guidance called Standard Evaluation Procedures (SEPs). Like the guidelines, unless elements in the SEPs are embedded in regulation, they are not mandatory. EPA has been attempting to upgrade the SEPs for the repellent studies for some time, and they should be completed soon. Standards for acceptable label claims are outside the scope of the guidelines. Data requirements are for tests of the duration of repellency using CPT.

The assumptions underlying the guideline have not changed since the fall 2008 when the Board reviewed the previous revision. EPA assumes that OPP will continue to require both laboratory and field tests (in some cases) for topical repellent efficacy. The guideline should include guidance concerning standard methods for commonly required types of testing, and does not need to address nonstandard methods. The guideline also should serve as a single source that would cover all of the ethical requirements of the new rule as well the scientific requirements.

Since the HSRB review in 2008, EPA has received HSRB comments on the guideline draft of September 2008 and on subsequently reviewed protocols and completed studies. Other comments have been received from registrants and investigators, colleagues at the U.S. Department of Agriculture (USDA), CDC, and other agencies that have an interest in insect repellents. The World Health Organization has issued final repellent testing guidelines, which EPA considered during the guideline revisions, and consumer research has been conducted to determine how users interpret language on repellent labels. EPA has compiled comments from the HSRB and other sources, and used a multidisciplinary internal workgroup to analyze comments by topic and issue. In early 2010, EPA consulted with repellent scientists from the USDA. Some of the recurring questions concerned policy issues; decisions made to resolve them were incorporated into the guidelines.

The guideline includes technical guidance for commonly required standard performance tests for skin-applied repellents and gives investigators the information necessary about the Human Studies Rule to prepare protocols and conduct studies likely to be reviewed favorably by EPA and the HSRB. The guideline does not include technical guidance for nonstandard or rarely performed tests, tests of the repellency of impregnated fabrics or clothing, or tests of repellents for indoor or outdoor spaces. Testing of the latter two kinds of repellency is less standardized than testing for topical repellents, and the guidelines for these tests are being drafted.

The guideline includes an introduction, definitions, and general guidance for all repellent studies organized around developing a protocol, protocol reviews, changes to approved protocols, and execution, reporting, and records retention. The section on developing a protocol includes scientific design, ethical justification, subject selection and informed consent, and protection of subject privacy and confidentiality. Sections of specific guidelines applying to commonly required tests are included, as are lists of references and appendices. Currently required standard tests in the guideline include laboratory tests to determine typical consumer dose and tests to determine CPT (such as laboratory tests with mosquitoes, laboratory tests with biting flies, field tests with mosquitoes, field tests with biting flies, and laboratory tests with ticks or chiggers). Earlier drafts included separate sections for the mosquito tests and biting fly tests, but there were few substantive differences between the two sections, and the sections were re-edited and combined in this draft. Guidance on laboratory tests with fleas also had been included in previous drafts, but contained anomalies that required correction; because tests with fleas are uncommon, it was deleted.

The current revision reflects policy decisions favoring tests for CPT that used confirmed failure events as endpoints and study designs that reduce the likelihood of data censorship and use K-M medians as the preferred statistic. Changes were made, as mentioned above, to streamline the organization of the document.

EPA made changes to simplify the general guidance, with most of the changes made in one of three topics: study design, statistical language used to analyze studies, and ethics with regard to prerequisite research. Changes were made to the study design guidance, including clarification that multiple treatments on the same subject are only appropriate in very limited cases. The guideline also recommends that treated subjects should not serve also as untreated controls because this produces confounding results. Because it is difficult to make meaningful comparisons between the results of different tests, from this point forward, EPA will recommend the use of positive controls in all studies; the positive control of preference is 20 percent DEET in ethanol at 1 g per 600 square cm. With this DEET data included, one set of study data can be calibrated against the next to determine if one repellent is more effective than another. The study design guidance further emphasizes the importance of representative samples to ensure that people were not arbitrarily excluded based on irrelevant and unjustified factors. Both sexes and a variety of races should be included. Additionally, the guideline recommends that subject attractiveness to target pests be established before they participate in the repellent testing.

Changes were made in the language about statistics to be used to analyze the studies. The guideline recommends longer test durations and earliest practical treatments to reduce the potential for data censorship. The discussion of sample size was changed from the 6 subjects required in the 1999 guidelines to the recommendation that a sample size be proposed and justified by a statistical rationale. The guideline does not offer fragmentary advice on what might influence sample size. EPA expects a statistical analysis plan that considers the distribution of the data, describes the methods of analysis contingent on this distribution, and uses the K-M median and CI, which is likely to coincide with the range of data points because of the sample sizes used in these studies.

Regarding ethics, changes were made to clarify the range of research that was prerequisite and to note that risks of concern are only those associated with participation in the research (not background risks). EPA has been less than satisfied with the focus and quality of the discussions about how benefits were distributed and how they relate to risk, so the guideline emphasizes that these discussions are required. In addition, the guideline recommends that subjects from potentially vulnerable populations should not be arbitrarily excluded if special care could provide adequate protection of their safety and welfare, and provides a rationale for discouraging distant travel. EPA has been concerned with the readability level of the materials provided to subjects, and cites the Flesch-Kincaid Grade Level as a measure of readability that investigators can use from Microsoft® Word to revise materials to lower the grade level. The guideline also asks investigators to specify how they will confirm subject candidates' understanding of the study.

EPA clarified methods for measuring subject skin area and calculating standard dose for dose determination studies, and identified additional reporting elements (such as an explicit calculation of a dose defined by weight-to-a-volumetric dose). On the laboratory tests for mosquitoes and flies, the guideline clarifies the discussion of rearing techniques, cage size, and insect density, and for field tests, clarifies subject placement and behavior. It also revises the site-selection criterion for mosquito studies for the pre-test absence of West Nile Virus to 2 weeks from 1 month so that investigators have more time to find a window of adequate mosquito activity. The guideline recommends a standard positive control, discourages the use of treated subjects as untreated controls, identifies additional reporting elements, and merges the mosquito and biting fly guidance. Changes also were made to the guidance on laboratory tests for ticks and chiggers, including clarification of the description of the recommended test method and refinement of the definition of "crossing" to suit the species and life stages used in testing. EPA had received comments that the 3-cm distance from the starting point to the boundary line and from the boundary line to the crossing line was inappropriate for nymphal ticks of some species that did not move fast or far. The guideline specifically accepts the idea of concurrent testing with two species; clarifies rearing techniques, number of ticks, test conditions, and subject preparation; and recommends standard positive controls (20 percent DEET).

EPA is eager to make the revised guideline available for use to supersede the 1999 guideline. The revision is a significant improvement on the old guideline, and fills critical gaps in the understanding of the Human Studies Rule and in what is required to receive a favorable review from the HSRB. The revision is in the final stages of internal review, and EPA expects to announce its availability for use in the *Federal Register* within the next few weeks. It will be published for use, but comments will be encouraged with no fixed comment period. EPA has learned a tremendous amount that has made the studies stronger scientifically and ethically, and will continue to learn from comments that will be reflected in guideline refinements. Mr. Sweeney and Dr. Clara Fuentes (OPP, EPA) did not have additional comments on the guideline.

Board Questions of Clarification

Dr. Philpott noted that some Board members had expressed points of concern earlier in the day that they wanted to raise during this discussion.

Dr. Young agreed that this guideline represents a step forward. As Mr. Jordan noted, when consumers read a label that states 6 hours of protection, they expect to be covered for 6 hours, but what is being published is stating that half the people will be protected for 6 hours, which is very different. She suggested that the proportion of population covered might be a better measurement of effectiveness. If the median is chosen, she asked how precisely the median is known, which relates to the sample size. The median must be measured with a specified degree of precision and to be conservative in the interest of the public, the lower bound of the CI should be used. The precision of the mean or median will need to be discussed by investigators. Sample size cannot be determined if this precision is not discussed. Removing the requirement for 6 subjects is a positive step, but Dr. Young expressed concern about how the sample size would be justified. Another point to note in the statistical analysis plan is that maximum likelihood methods require that the distribution be known. EPA should strike the point stating that if the data do not fit and cannot be transformed to fit an underlying distribution, maximum likelihood estimates are suggested, because that is inappropriate.

Dr. Popendorf commented that the statements made on using "must" versus "should" were well taken, but that acute toxicity testing perhaps should be a "must" rather than a "should." A chemical should never be tested without having acute toxicity data. The guideline has some points that should be changed, because they perhaps are too specific. Inconsistencies with the study CLBR conducted exist in the guideline regarding ticks. There are difficulties trying to envision how subjects would put their fingers on flat surface and have their forearms upright. He expressed uncertainty about USDA's concerns about positive controls, and asked what value they might have in the LNX-002 study. Positive controls impose more exposures on people, and although they may have some benefits, are recommended too strongly in the guideline without clear justification. The focus of the guideline is on CPT, and in some ways that is a misnomer, because there are landings within CPT. The market survey indicates that the public is interested in CPT, but CPT really is not complete, so it would be useful to know the real level of protection during CPT. The rates of bites of the untreated controls could be compared to the rates of bites of the treated subjects. Data on the unconfirmed landings are available, and the calculations could be made. The guidelines mention relative protection and percent repellency, but they really are not defined and should be. Dr. Popendorf presented the following calculations as suggestions:

- unprotected insect activity = total number of LIBes among controls / total person X minutes they were exposed
- protected insect activity = total number of LIBes among subjects / total person X minutes they were exposed
- repellent effectiveness (% reduction) = 100 X (1-protected insect activity / unprotected insect activity)
- repellent effectiveness (relative protection) = unprotected insect activity / protected insect activity

With the cream repellant in LNX-002, there was 1 bite per minute and 14 landings in 397 minutes, which would be a protection factor of 28, and that would be the relative protection. An improvement in the protocols would be to measure the time that it takes for the unprotected subjects to be bitten, which gives a second measure in addition to the CPT. The protection during that time could be estimated. The current calculations are not really serving the public as well as

they could. There are only two unprotected controls versus 10 protected subjects, so on that basis it is an unbalanced design, but if landings are examined, it is 397 to 14, with many more bites among a smaller population. It is possible that if examined from the right perspective, the frequency of the unprotected subjects would balance the numbers of the protected subjects to give a reasonable power to that calculation.

Dr. Johnson stated the positive controls should be discussed, and asked how the data would be used and how many subjects must be assigned to the positive control group. He asked, if one of the two studies examined at the meeting were considered, how decisions would have been made differently depending on what the positive control showed. If the positive control is working and the test product is not, the data will likely not be submitted. In terms of median protection time, the Board does not know how the information from these studies translates into the regulating or the labeling processes.

Dr. Lebowitz commented that a positive control is a gold standard. In current clinical trials, a placebo cannot be used, so a positive control is employed. Dr. Johnson noted that a positive control conducted for comparison purposes could be useful. Perhaps Dr. Popendorf was asking why USDA would impose their arguments for including positive controls on EPA.

Dr. Chambers noted that repellent efficacy varies with environmental conditions, so perhaps the positive control is being used to adjust data upward or downward depending on those conditions. If that is the case, a full complement of subjects is needed in the positive control to obtain accurate numbers. She expressed confusion as to how the positive control would be used. It must be ensured that the design is sufficient to use the positive control. She asked if different laboratories apply different amounts of the same product, how this comparison will be handled for labeling purposes.

Mr. Jordan remarked that Dr. Johnson indicated that the Board is missing information about how the data are translated to labeling. The SEPs will deal with this issue. EPA is examining making adjustments to the data to reflect the variability between test sites and laboratories by using a consistent positive control across studies. EPA will re-examine the number of subjects. At first, EPA will not have the ability to do much with the positive controls because many studies will not have used them, but as time passes, there should be sufficient studies to offer some sense of the variability and allow some adjustments to be made. The same thing may happen with typical consumer dose data sets. The variables that determine the dose include formulation, the amount dispersed through the aperture, and the individual preferences about how much to apply. As EPA sees more results, there may be a convergence in data. Viscosity and pressure of the formulation are factors in how much will be applied. These data need to be collected now to allow comparisons at some point in the future.

Mr. Carley responded to a question about how positive control data would affect EPA's review. It probably will affect EPA's review in the near term; however, another policy objective is to provide a basis for specific label claims of protection and improve repellent labeling for consumers. It is in that endeavor that EPA will be able to make use of positive control data because it allows a much better comparison of the products to each other if calibrated against 20 percent DEET. As of now, there is no basis for interpreting a comparison of the results of two

different studies because there is no common thread. If the same product is tested two different times with the same protocol but under different circumstances and the results are different, it is unclear whether the CPT actually is changing. Much information is available on DEET performance, and if a specific study can be tied back to this information, EPA will have greater ability for comparison.

Dr. Chambers expressed appreciation to EPA for including many HSRB opinions in the new guideline. She asked how verifying the attractiveness of study candidates to target species is determined for the field studies, and whether it was conducted before the study commenced or during the trial.

Dr. Carroll noted that verifying attractiveness was conducted for the first time by CLBR in the black fly study, LNX-002. In this case, it was conducted in the field just prior to the trials using the subject's untreated arm. Dr. Chambers inquired if the subjects already had been treated at that time. Dr. Carroll responded that they had been treated, so there was potential for interaction, but it would potentially decrease rather than increase attractiveness. Dr. Popendorf asked if all the subjects tested positive for attractiveness, and Dr. Carroll replied that they did.

Dr. Gamble noted that the guideline states that the attractiveness of recruited candidates to the target species should be verified before they participate in repellency testing. Mr. Carley commented that EPA inserted this statement in the guideline because it would be advantageous to some companies to recruit subjects that are not attractive to the target species. In the scenario that Dr. Carroll described, the attractiveness test was conducted before the repellency trial, and it was not a difficult modification. It was added in the amendment after the HSRB discussion of the LNX-002 protocol. Dr. Gamble inquired if it is the expectation of EPA that verifying attractiveness should be conducted before every study. The discussion in the guideline moves from demographics to this statement on verifying attractiveness. Mr. Jordan responded that certain elements of the guidelines are expressed as "shoulds" because they are not legally enforceable or binding, and the failure to conduct them may not be a fatal flaw in the execution of the study. Data generated from a study that did not follow a "should" might still satisfy EPA and be used in its regulatory decision-making.

Dr. Gamble questioned if it is an important part of having a representative sample to have attractiveness verified beforehand. Dr. Popendorf asked whether it would be better to have unattractiveness to the target species as an exclusion criterion. Mr. Carley responded that if it were an exclusion criterion, it would have to be determined before a subject was enrolled in the trial, and if it has to be done in the field, subjects need to be fully enrolled. Dr. Prentice quoted the guideline that states that EPA "recommends tests in attractiveness to target pests to qualify," and observed that the Agency may want to reword this to be clear that subjects are already enrolled when the testing occurs. Dr. Sharpe asked if lack of attractiveness was a stop rule now. Mr. Jordan responded that the Agency did not have a lot of experience in determining how this would be implemented. It has not been conducted often in field trials, but has been done more in laboratory testing.

Dr. Philpott noted that part of the confusion on the issue may be a result of where it is placed in the document. It occurs in the ethics section, but it is really a question fundamental to

the scientific design and conduct of the study. It is a key inclusion criterion, but Dr. Philpott also raised the question of why it was in that particular location in the document. Mr. Carley responded that there were not separate science and ethics sections; representativeness spans the boundary. Dr. Philpott stated that it may be necessary to reorganize the section. Mr. Jordan noted that EPA would re-examine the wording. Dr. Johnson added that the statement should be that attractiveness should be verified and should not include "before they participate."

Dr. Chambers referenced a study with mosquitoes in a cage that stopped biting well so they were replaced, and asked if this would still be a legitimate action. Mr. Carley noted that the relevant passage is the specific guidance for laboratory studies of mosquitoes and biting flies, section J7 about insect density, under establishing and confirming landing pressure, section 13, which states, "if at any time fewer than five mosquitoes land on the untreated control forearm within one minute, all mosquitoes should be removed from cages and fresh insects should be added to each cage." This is suggested to maintain acceptable threshold pressure in a cage study.

Dr. Chambers noted that if investigators want to get the number of landings in the untreated control, subjects will have to be exposed for the full 1-minute period, the same as the treated subjects. Dr. Popendorf added that when untreated controls receive their first landing, if the time of landing is recorded, that will give the landing frequency as well. Dr. Young stated that that was making an assumption about distribution of time until the first landing, which is a very different endpoint than the number of landings in the specified time. The number of times versus the time to first event are quite different things, and the distribution would be different. Dr. Philpott suggested tabling the discussion until a later time as there is insufficient time to obtain statisticians' opinions at the current meeting.

Dr. Green asked if the guideline, because it would be published for immediate use, would be open for public comment. Mr. Carley responded that EPA's intention is to release them for use and invite comment. The two laboratories that have conducted chemical repellent efficacy trials since 2006 are both very familiar with what the guideline says, but many other laboratories have not submitted anything for the HSRB because there are misconceptions about what the laboratories need to do to produce a satisfactory proposal under the Human Studies Rule. EPA believes it is very important to release the guideline because people need the information.

Dr. Green noted Dr. Chambers' last question to Mr. Jordan clarified some ambiguousness regarding positive controls, and urged the EPA to recognize the hot button issues that raise HSRB concerns and consider careful review or analysis of those points and the rationales for them. He further noted that nymphal ticks may move slower than other ticks and this may influence the results of the study. In most toxicology studies, one of the first things seen in a guideline is the age and weight of animals to bring uniformity to the population. Nonuniformity can lead to variability; Dr. Green asked if that was an issue that should be examined. He asked if there are seasonal variations in terms of biting flies, and whether younger and older flies bite in certain seasons. If a field study is conducted in a certain season, then only a portion of the population is being tested, and he asked if this should be considered. Mr. Carley responded that it has been considered in the specific guidance for laboratory studies for mosquitoes and flies; it is not relevant for field studies because the fly and mosquito populations can only be controlled in the laboratory. Paragraph J2 concerns age, stage, and sex, and states that mosquito testing should

be conducted with adult females 5 to 10 days old; methods of sexing should be reported; stable flies should be male or female adults 3 to 10 days old; and the age range of test insects should be reported. In the ticks studies, under stage, age, and sex, it states that when testing with black-legged ticks, deer ticks, lone star, or softback ticks, either adult or nymphal life stages are appropriate; only the adult American dog tick is recommended since nymphs of this species do not feed on humans; tests with chiggers should use immature chiggers; and age or age range of all animals should be reported.

Dr. Green referenced SEPs and inquired when these were used. Mr. Carley noted that the sequence he detailed was data requirements established by regulation and test guidelines that provide investigators and sponsors with advice about how to conduct a test and meet those data requirements. After EPA has received the test, SEPs are EPA's standard operating procedures for how to review it. The framework for protocol analysis, including the matrix of questions is evidence of a standard evaluation approach, but EPA does not have an SEP for protocol review. SEPs are internal procedures that dictate the types of summary tables that should be built, the standard of completeness, and so on.

Dr. Philpott noted that the Board was running behind schedule and that there were many comments because no specific charge question had been asked. Because the guideline will be open for comments, there are additional mechanisms that can be used to make recommendations to the Agency. If members have additional concerns or questions, they can be compiled and discussed on the teleconference to be held to finalize the meeting report, or members can submit comments directly to the Agency as individuals.

Dr. Gamble pointed out several issues on pages 13 and 14 of the guideline, and noted that many of her comments stem from her work with clinical trials, although she realizes that these studies are different. Her comments regard racial and ethnic minorities and recruitment strategies and issues surrounding vulnerability. "Race/ethnicity" should be the term used instead of "race." When vulnerability is discussed, the issues at hand are not only avoiding arbitrary exclusion if provisions can be made to ensure the safety of the participants, but also concern potential benefits from the research to the vulnerable groups. Regarding methods of recruitment, it was suggested that the Agency examine the Board's last report, which discusses the issue of language. Specific dialects also must be considered when materials are translated for candidates. The Department of Health and Human Services has whole class standards that are culturally and linguistically appropriate. Recruitment also should be conducted in Spanish if the study is being conducted in certain areas to ensure that there is a broad recruitment strategy that covers the entire population. On page 14, number III, the guideline states that if any candidates may prefer to speak or read a language other than English, procedures for accommodating them need to be adopted in the recruiting process. Researchers should be urged to examine the recruitment population in advance so that speakers of other languages are present when needed.

Dr. Philpott observed that the Agency appreciates the comments, and reiterated that if members have additional comments, they should be sent to him, and he will compile them for the report and send them to the Board. Members also should feel free to submit comments as members of the public. Dr. Gamble asked if members send comments to the Agency on the guideline, whether they were to be submitted as members of the Board or as individuals. Dr.

Philpott responded that individual comments sent to the Agency were not to be submitted with Board affiliation so that they would not be taken to reflect HSRB consensus, but those comments sent to him would be from the Board.

OPP Presentation: Settlement Agreement in Litigation Against EPA's Human Studies Rule

Mr. Jordan noted that in the late 1990s, EPA was at the center of a controversy regarding the types of human testing with pesticides that were ethically and scientifically acceptable. The controversy today is less significant than in the past, and EPA hopes that the settlement agreement with its regulatory changes will reduce worries among stakeholders.

At issue in the litigation is EPA's 2006 rule, "Protections for Subjects in Human Research." Modeled on the Common Rule, it applied to third-party research involving intentional exposure of human subjects submitted to EPA under the pesticide laws and prohibited such research on children and pregnant or nursing women from consideration in EPA decision-making; EPA also is forbidden to conduct any research involving exposure of children and pregnant or nursing women. Other adults who voluntarily choose to participate in research would be protected under the rule, which required that the protocols for proposed research be reviewed by EPA and the HSRB. (The rule also established the Board.)

Natural Resources Defense Council, Inc., Pesticide Action Network of North America, Pineros y Campesinos Unidos del Noroeste, Physicians for Social Responsibility, Farm Labor Organizing Committee of the AFL-CIO, and Migrant Clinicians Network filed the lawsuit against EPA in the spring of 2006, shortly after the rule was published. The organizations were joined in the litigation by Senators Barbara Boxer (D-CA) and Bill Nelson (D-FL) and Representatives Henry Waxman (D-CA 30th District) and Hilda Solis (D-CA 32nd District) who filed as *amici curiae* in support of the petitioners.

The petitioners argued that the rule did not go far enough to protect subjects, and that the scope was inconsistent with the requirements of the 2006 Appropriations Act, which included a provision that states that "none of the funds made available by this Act may be used by the Administrator of EPA to accept, consider, or rely on third party intentional dosing in human toxicity studies for pesticides or to conduct intentional dosing in human toxicity studies with pesticides, until the Administrator issues a final rule on the subject. Such rule shall not permit use of pregnant women, infants, or children as subjects. It shall be consistent with the principles proposed in the 2004 report of the NAS on intentional human dosing and the principles of the Nuremberg Code with respect to human experimentation, and shall establish an independent Human Subjects Review Board." EPA met the 180-day deadline for the rule, but the petitioners said that the substance of the rule issued was not consistent with the principles in the 2004 NAS report or the principles of the Nuremberg Code.

After filing the challenge to the regulation, all parties submitted briefs and oral arguments before the U.S. Court of Appeals for the Second Circuit in New York City in fall 2006 through January 2008. In April 2009, under direction of the Agency's leadership, EPA began settlement negotiations that lasted through June 2010. The settlement agreement was filed on June 18, 2010,

and is available at http://www.epa.gov/oppfead1/guidance/human-studies-settlement.pdf. EPA has filed papers with the court asking that the case be stayed to allow the Agency to implement the settlement agreement. The court has not yet ruled on this, but EPA is confident that it will stay the case.

The settlement agreement states that EPA will undertake rulemaking to change the 2006 rule, defines the schedule for conducting the rulemaking, and contains an attachment with exact negotiated rule language to be proposed for public comment. If EPA does not comply in the timeframe negotiated with a proposed rule that includes the negotiated language, the petitioners can reopen the lawsuit. EPA has negotiated amendments to the rule that address the petitioners' core legal challenges: the scope to cover all EPA regulatory statutes; consistency with NAS recommendations; and consistency with the Nuremberg Code.

The 2006 rule applies to research involving intentional exposure of a human subject; intended for consideration under the pesticide laws (40 CFR part 26, subparts K, L, and M); or relied on by EPA under the pesticide laws (40 CFR part 26, subparts P and Q). EPA did not specify the type of substance to which a subject might be exposed. The Agency drafted the rule with the understanding that any third-party research involving intentional exposure of human subjects submitted to be considered under the pesticide law would be covered by the rule. The petitioners thought that the rule text left a loophole for unethical human research to be conducted with pesticides and relied on by EPA under other statutes such as the Clean Water Act, Clean Air Act, or the Superfund law, and that those studies would not be covered by the 2006 rule. In consideration of this concern, EPA will propose that subpart K "applies to all research initiated after [effective date of amended rule] involving intentional exposure of a human subject *to a pesticide* if ... any person who conducted or supported such research intended ... to submit results of the research to EPA for consideration *in connection with any action that may be performed by EPA under any regulatory statute administered by EPA* ..." (new language is italicized). Similar changes will be made to 40 CFR part 26, subparts L, M, and Q.

The amended rule clearly would apply to research with pesticides submitted under FIFRA or the Federal Food, Drug, and Cosmetic Act, which is not a change, but the rule would only apply for research considered by EPA under other regulatory statutes if it were conducted with a pesticide. "Pesticide" is defined in the rule as a substance or mixture intended for pesticidal effect. All of the studies the HSRB has considered in the past four years were clearly conducted with a pesticide and fall under the scope of this rule. Other studies could be conducted in which a pesticide is not used as a pesticide, such as dermal absorption studies in a risk assessment. Even if the research involves a substance not being used as a pesticide, EPA will still consider it a pesticide if human exposure results mainly from its use as an active ingredient in a pesticide. If a study were conducted with atrazine on dermal absorption, for example, that would be a human study within the scope of this rule. The rule would not apply to multi-use chemicals that can be used as a pesticide unless they are being tested as a pesticide. Formaldehyde, for example, is registered as a pesticide, but also is used as a materials preservative and as a binding agent in pressed wood products. In the past, scientists have conducted research on off-gassing of formaldehyde in residences in which human subjects were intentionally exposed to the chemical. If similar studies are conducted in the future, they would fall outside the scope of the rule, because formaldehyde is not being used as a pesticide in such tests. Some chemicals that are

pesticides also are used as therapeutic drugs, and a test of their therapeutic benefits would not be considered a test of a pesticide. Also, ubiquitous environmental chemicals, such as sulfur dioxide, fall outside the scope of the rule. Although none of these studies would be subject to the protocol review requirements of subpart K, if EPA wanted to rely on these studies under 40 CFR part 26, subpart Q, EPA would review the studies for ethical and scientific acceptability and bring them to the HSRB. EPA expects very little impact from this change, because the Agency has seen no study in the past 4 years "involving intentional exposure of a human subject to a pesticide" that was not covered by the 2006 rule.

In terms of consistency with the NAS principles, the 2006 rule followed the NAS recommendation to start from the Common Rule to protect subjects of third-party research involving intentional exposure. The NAS document did not contain "principles," but contained 17 recommendations. The petitioners argued that these should have been included in the rule, and because they were not, the rule was inconsistent with NAS principles. EPA will propose in subpart P (which involves EPA and HSRB review of protocols and completed studies), additional directions about what should be reviewed.

Regarding science, EPA will propose language directing the Agency to consider:

- whether the research is likely to produce data that addresses an important scientific policy question that cannot be answered with animal data or human observational research;
- the appropriateness of research design as related to current scientific standards;
- representativeness of the study participants;
- statistical adequacy of the study design; and
- whether the investigators propose to conduct the research in accordance with good research practices and safety monitoring requirements.

In each case, the new language would not set a standard for acceptability, but would direct EPA to consider these issues in the overall assessment of the scientific soundness of the proposed and completed research. The list is a set of considerations rather than standards.

Proposed changes in ethics will require EPA to consider in protocol review:

- adequacy of previous animal studies;
- adequate identification and minimization of subject risks;
- appropriate balance of risks and benefits;
- equitable subject selection;
- free and fully informed consent;
- IRB review and approval;
- adequate protection for potentially vulnerable subjects;
- adequate protection for potentially sensitive subjects;
- appropriate and non-coercive payments to subjects; and
- provision of medical care for research-related injuries.

All are topics that reviews conducted by EPA and the Board have addressed. EPA and the Board will need to ensure that written reviews in the future specifically address each of these 10

elements, but they are not a departure from the standard review approach. These are factors to consider rather than standards.

When the 2006 rule was issued, like the Common Rule, it allowed for a "legally authorized representative" to consent on behalf of a test subject who lacks the capacity to provide informed consent. Petitioners challenged this inclusion as inconsistent with the Nuremberg Code, which states that: "The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent." In response, EPA will delete the references to surrogate consent, which will affect four provisions: the definition of legally authorized representative; the criteria for IRB approval; the general requirements for informed consent; and the documentation of informed consent. EPA expects these changes to have negligible impact, because the Agency has not seen any studies that would permit consent from a legally authorized representative.

New provisions will be proposed that will affect the HSRB. In HSRB review of proposed and completed human research, 40 CFR §26.1606, the Board will be directed to examine the same sets of considerations that EPA is required to examine under the new rule; 40 CFR §26.1603(d) states that EPA can impose additional conditions on proposed research, and if it does, the HSRB will be required to examine them as well.

Some of the NAS recommendations dealt with acceptance standards, and state how EPA should judge the ethical and scientific acceptability of completed research. EPA will be proposing to make changes to those parts of the 2006 rule that articulate acceptance standards. EPA will propose to revise the substantive standards for relying on covered, completed research, adding a categorical prohibition against reliance on "scientifically invalid research" or data that are not "relevant to a scientific or policy question important for EPA decision-making." Four specific science issues will need to be examined: whether research was designed and conducted in accordance with appropriate scientific standards; the extent to which the research subjects are representative of populations; the statistical power of the research; and (in a study that reports a no observed effect level or a no observed adverse effect level) whether there was a level that gave rise to a biological effect thus demonstrating that the study had sensitivity. These four points are considerations, not standards.

In terms of standards for ethical acceptability, 40 CFR §26.1704 articulates the standards for studies initiated prior to the promulgation of the 2006 rule, but the ideas apply to newer studies as well. Changes to the following text were made (deletions are in strikethrough and additions are in italics): EPA should not rely on research "if there is clear and convincing evidence that the conduct of the research was fundamentally unethical (e.g., the research was intended to seriously harm participants or failed to obtain informed consent) or was ~~significantly~~ deficient relative to the ethical standards prevailing at the time the research was conducted *in a way that placed participants at increased risk of harm (based on knowledge available at the time the study was conducted) or impaired their informed consent.*" The added verbiage is similar to those in the guidance developed by the HSRB when it first started to apply the 2006 rule and 40 CFR §26.1704 to completed studies. EPA considers this a useful clarification consistent with the practice that the Board has been following for the past 4 years, and the petitioners believed it was an improvement. EPA will propose parallel changes to 40 CFR §26.1705, where the word

"substantial" will be deleted from in front of "compliance to subparts A through L" and replaced with verbiage to the effect that if any noncompliance resulted in placing participants at increased risk of harm, or impaired their informed consent, that would make the study unacceptable. EPA expects no impacts on third parties or on the HSRB from the changes to 40 CFR part 26, subparts P and Q. The changes will require more detail in EPA's scientific and ethical reviews.

The changes would apply prospectively once the final rule takes effect. EPA may propose some additional changes to correct minor errors that will not substantively affect third parties, EPA, or the HSRB, and may make changes, such as revising the organization of the rule or adding references to guidance documents. The proposed rule is expected to be signed by January 18, 2011, and published for public comment. After the comment period ends, the comments will be analyzed and EPA will promulgate a signed final rule by December 18, 2011. Although EPA has agreed in the settlement to release a proposal that follows the substance of the settlement agreement, the settlement is clear that EPA retains discretion not to adopt any of the changes if, after consideration of public comments, the Agency believes it would be unwise to do so. Until the final rule is promulgated, the 2006 rule will remain in effect.

Board Questions of Clarification

Dr. Philpott suggested an abbreviated 15-minute discussion, keeping in mind that comments can be incorporated into the meeting report and discussed via teleconference as well. Additionally, since the proposed rule will be published, Board members can comment as private citizens during the rule's comment period.

Dr. Sharpe asked if December 2011 was the rule due date under the settlement. Mr. Carley responded that it was; the settlement states that the proposal is due out 7 months after it was filed with the court (January 18, 2011) and that the final rule is due 11 months after that (December 18, 2011).

Dr. Philpott inquired if the plaintiffs will be involved in discussions about the public comments and how to amend the final rule. Mr. Jordan explained that the plaintiffs are entitled to comment like any member of the public. Court decisions exist about the extent to which discussions can be conducted between a specific member of the public and an agency during the course of rulemaking, and these discussions are discouraged. No decision has been made at this point as to how discussions with the plaintiffs will be handled. Mr. Carley added that nothing in the settlement agreement gives the plaintiffs any role in the rulemaking process.

Dr. Prentice questioned how the six plaintiffs joined together. Mr. Jordan replied that all of the organizations have followed EPA's pesticide regulation activities. Mr. Carley added that all of the organizations had been involved in the controversy about pesticides that had preceded the rule, and had commented that EPA had not gone far enough. Dr. Prentice expressed interest in the fact the Nuremberg Code had been used, because it is not used often in litigation; he understands that the Nuremberg Code makes no provision for surrogate consent. Mr. Jordan noted that the petitioners cited the Nuremberg Code because it is cited in the 2006 Appropriations Act; other issues in the Nuremberg Code were discussed, but only one has been changed based on negotiations.

Preview of Upcoming Meetings

Ms. Kelly Sherman (OPP, EPA) listed the topics expected for the HSRB's October 2010 meeting, which will likely be a multi-day meeting.

- From the Agricultural Handlers Exposure Task Force (AHETF), a new protocol for an applicator exposure study for utility rights of way examining two application methods: backpack application of liquid spray, and handgun application at a distance from a truck.
- Also from the AHETF, two completed studies and the associated monograph: the closed cab air blast study and the open cab air blast study, both of which were reviewed by the Board in 2008.
- From the AEATF, a completed mop study. The protocol was reviewed by the Board in 2008.
- From CLBR, a new protocol on a mosquito field study with a new active ingredient, eucalyptus extract and oil of lemon in one formulation.

Mr. Downing noted that the next meeting would be held October 26-29, 2010; members should hold those dates and will be informed of exact dates as the meeting approaches.

Closing Comments

Dr. Philpott closed the meeting by thanking members for their work and noting that he looked forward to meeting with them via teleconference. He will send an e-mail to try to schedule the teleconference within the next few months.

Dr. Philpott adjourned the meeting at 5:25 p.m.

Respectfully submitted:

Jim Downing
Designated Federal Officer
Human Studies Review Board
United States Environmental Protection Agency

Certified to be true by:

Sean Philpott, Ph.D., M.S. Bioethics
Chair
Human Studies Review Board
United States Environmental Protection Agency

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

Attachments

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

Attachment A

EPA HUMAN STUDIES REVIEW BOARD MEMBERS

Chair

*Sean Philpott, PhD, MS Bioethics — Term: 3/27/2006-10/31/2011
Director, Research Ethics
The Bioethics Program
Union Graduate College-Mt. Sinai School of Medicine
Schenectady, NY

Vice Chair

*Janice Chambers, Ph.D., D.A.B.T. — Term: 3/27/2006-10/31/2011
William L. Giles Distinguished Professor
Director, Center for Environmental Health Sciences
College of Veterinary Medicine
Mississippi State University
Mississippi State, MS

Members

*George C.J. Fernandez, Ph.D. — Term: 5/1/2010-8/31/2013
Director, Center for Research Design and Analysis
University of Nevada – Reno
Reno, NV

*Vanessa Northington Gamble, M.D., Ph.D. — Term: 10/19/2009-10/31/2012
University Professor of Medical Humanities
Gelman Library
The George Washington University
Washington, DC

*Sidney Green, Jr., Ph.D., Fellow, ATS — Term: 10/19/2009-10/31/2012
Department of Pharmacology
Howard University College of Medicine
Howard University
Washington, DC

*Dallas E. Johnson, Ph.D. — Term: 8/31/2007-8/31/2013
Professor Emeritus
Department of Statistics
Kansas State University
Manhattan, KS

*Michael D. Lebowitz, Ph.D., FCCP — Term: 3/27/2006-8/31/2012
Retired Professor of Public Health
(Epidemiology) & Medicine & Research Professor of Medicine
University of Arizona
Tucson, AZ

*^José E. Manautou, Ph.D. — Term: 5/1/2010-8/31/2013
Associate Professor of Toxicology
Department of Pharmaceutical Sciences
School of Pharmacy, University of Connecticut
Storrs, CT

Jerry A. Menikoff, M.D. — Term: 3/27/2006-8/31/2012
Director, Office for Human Research Protections
Department of Health and Human Services
Rockville, MD

*^Rebecca Tyrrell Parkin, Ph.D., MPH — Term: 10/1/2007-8/31/2013
Associate Dean for Research and Public Health Practice
School of Public Health and Health Services
The George Washington University
Washington, DC

*William J. Popendorf, Ph.D. — Term: 10/19/2009-10/31/2012
Professor
Department of Biology
Utah State University
Logan, UT

*Ernest D. Prentice, Ph.D. — Term: 10/1/2007-9/30/2010
Associate Vice Chancellor for Academic Affairs
Professor of Genetics, Cell Biology and Anatomy
Professor of Preventive and Societal Medicine
Omaha, NE

Virginia Ashby Sharpe, Ph.D. — Term: 5/1/2010-8/31/2013
National Center for Ethics in Health Care
Veterans Health Administration
Department of Veterans Affairs
Washington, DC

*Linda J. Young, Ph.D.
Department of Statistics
Institute of Food and Agricultural Sciences
University of Florida
Gainesville, FL

Term: 3/28/2008-8/31/2012

*Special Government Employee (SGE)
^Not in attendance at the June 23, 2010 Meeting

Attachment B

Federal Register Notice Announcing Meeting

[Federal Register: June 8, 2010 (Volume 75, Number 109)]
[Notices]
[Page 32461-32463]
From the Federal Register Online via GPO Access [wais.access.gpo.gov]
[DOCID:fr08jn10-91]

ENVIRONMENTAL PROTECTION AGENCY

[EPA-HQ-ORD-2010-0381; FRL-9159-9]

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 research with human subjects.

DATES: The public meeting will be held on June 23, 2010, from approximately 10 a.m. to approximately 5:30 p.m., Eastern Time.

Location: Environmental Protection Agency, Conference Center—Lobby Level, One Potomac Yard (South Bldg.), 2777 S. Crystal Drive, Arlington, VA 22202.

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 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 section I., under subsection D., SUPPLEMENTARY INFORMATION of this notice.

FOR FURTHER INFORMATION CONTACT: Any member of the public who wishes further information should contact Jim Downing, EPA, Office of the Science Advisor, (8105R), Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460; telephone number: (202) 564-2468; fax: (202) 564-2070; e-mail addresses: downing.jim@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-2010-0381, 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 20460. The hours of operation are 8:30 a.m. to 4:30 p.m. Eastern Time, Monday through Friday, excluding Federal holidays. Please call (202) 566-1744 or e-mail the ORD Docket at ord.docket@epa.gov for instructions. Updates to Public Reading Room access are available on the Web site (http://www.epa.gov/epahome/dockets.htm).

Instructions: Direct your comments to Docket ID No. EPA-HQ-ORD-2010-0381. 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 the disclosure of which 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, especially 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 20460. The hours of operation are 8:30 am to 4:30 p.m. EST, Monday through Friday, excluding Federal holidays. Please call (202) 566-1744 or e-mail the ORD Docket at ord.docket@epa.gov for instructions. Updates to Public

Reading Room access are available on the Web site (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 early June 2010. 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 Web site and the EPA HSRB Web site 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:

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

D. How may I participate in this meeting?

You may participate in this meeting by following the instructions in this section. To ensure proper receipt by EPA, it is imperative that you identify docket ID number EPA-HQ-ORD-2010-0381 in the subject line on the first page of your request.

1. Oral comments. Requests to present oral comments will be accepted up to June 16, 2010. To the extent that time permits, interested persons who have not pre-registered may be permitted by the Chair of the HSRB to present oral comments at the meeting. Each individual or group wishing to make brief oral comments to the HSRB is strongly advised to submit their request (preferably via e-mail) to the person listed under FOR FURTHER INFORMATION CONTACT no later than noon, Eastern Time, June 16, 2010, 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.

2. Written comments. Although you may submit written comments at any time, for the HSRB to have the best opportunity to review and consider your comments as it deliberates on its report, you should submit your comments at least five business days prior to the beginning of the meeting. If you submit comments after this date, those comments will be provided to the Board members, but you should recognize that the Board members may not have adequate time to consider those comments prior to making a decision. Thus, if you plan to submit written comments, the Agency strongly encourages you to submit such comments no later than noon, Eastern Time, June 16, 2010. You should submit your comments using the instructions in section I., under subsection C., "What should I consider as I prepare my comments for EPA?" above in 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

1. Topics for discussion. The HSRB is a Federal advisory committee operating in accordance with the Federal Advisory Committee Act (FACA) 5 U.S.C. App. 2 section 9. The HSRB provides advice, information, and recommendations to EPA on issues related to scientific and ethical aspects of human subjects research. The major objectives of the HSRB are to provide advice and recommendations on: (1) Research proposals and protocols; (2) reports of completed research with human subjects; and (3) how to strengthen EPA's programs for protection of human subjects of research. The HSRB reports to the EPA Administrator through EPA's Science Advisor.

At its meeting on June 23, 2010, EPA's Human Studies Review Board will consider scientific and ethical issues surrounding these topics:

(a) The unpublished report of the completed Carroll-Loye Biological Research, Inc. study LNX-002: Field Repellency of Two Picaridin-Based Personal Insect Repellents to Black Flies. The protocol for this study was reviewed favorably by the HSRB at their meeting in June 2009. EPA seeks the advice of the HSRB on the scientific soundness of this completed study for use to estimate the duration of complete protection against black flies provided by the tested repellents, and on whether available information supports a determination that the study was conducted in substantial compliance with subparts K and L of 40 CFR part 26.

(b) The unpublished report of the completed Carroll-Loye Biological Research, Inc. study LNX-003: Laboratory Repellency of Two Picaridin-Based Personal Insect Repellents to Two Species of Ticks. The protocol for this study was reviewed favorably by the HSRB at their meeting in October 2009. EPA seeks the advice of the HSRB on the scientific soundness of this completed study for use to estimate the duration of complete protection against ticks provided by the tested repellents, and on whether available information supports a determination that the study was conducted in substantial compliance with subparts K and L of 40 CFR Part 26.

(c) In addition, EPA will present to the HSRB update reports on two topics of interest:

(1) The revised guideline for performance testing of topically applied repellent products, for use by investigators and sponsors of new studies

(2) The terms of a recent settlement of litigation related to EPA's 2006 rule for the protection of human subjects of research, in which EPA has agreed to initiate rulemaking to amend the 2006 rule.

2. 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 report, if applicable, can be found at http://www.epa.gov/osa/hsrb/ or from the person listed under FOR FURTHER INFORMATION CONTACT.

Kevin Teichman,
EPA Science Advisor.
[FR Doc. 2010-13684 Filed 6-7-10; 8:45 am]
BILLING CODE 6560-50-P

Attachment C

U.S. ENVIRONMENTAL PROTECTION AGENCY
HUMAN STUDIES REVIEW BOARD
JUNE 2010 PUBLIC MEETING

Environmental Protection Agency Conference Center
Lobby Level - One Potomac Yard (South Bldg.)
2777 S. Crystal Drive, Arlington, VA 22202

JUNE 23, 2010

10:00 AM **Convene Meeting and Administrative Procedures** – Mr. Jim Downing (Designated Federal Officer, EPA Human Studies Review Board [HSRB], Office of the Science Advisor [OSA])

10:05 AM* **Introduction and Identification of Board Members** – Sean Philpott, Ph.D. (HSRB Chair)

10:15 AM **Welcome** – Pai-Yei Whung, Ph.D. (Chief Scientist, OSA, EPA)

10:20 AM **Opening Remarks** – Steven Bradbury, Ph.D. (Director, Office of Pesticide Programs [OPP], Office of Chemical Safety and Pollution Prevention, EPA)

10:25 AM **EPA Follow-up on Previous HSRB Recommendations** – Mr. William Jordan (OPP, EPA)

Completed Carroll-Loye Biological Research, Inc. (CLBR) Study LNX-002: Field Repellency of Two Picaridin-Based Personal Insect Repellents to Black Flies

10:30 AM **EPA Science and Ethics Reviews** – Mr. Kevin Sweeney (OPP, EPA) and Mr. John Carley (OPP, EPA)

11:00 AM **Board Questions of Clarification** – Sean Philpott, Ph.D. (HSRB Chair), EPA, Principal Investigator/Sponsor

11:30 AM **Public Comments**

11:45 AM **Board Discussion**

Charge to the Board:

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

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

12:15 PM **Lunch**

Completed Carroll-Loye Biological Research, Inc. (CLBR) Study LNX-003: Laboratory Repellency of Two Picaridin-Based Personal Insect Repellents to Two Species of Ticks

1:15 PM **EPA Science and Ethics Reviews** – Mr. Kevin Sweeney (OPP, EPA) and Mr. John Carley (OPP, EPA)

1:45 PM **Board Questions of Clarification** – Sean Philpott, Ph.D. (HSRB Chair), EPA, Principal Investigator/Sponsor

2:15 PM **Public Comments**

2:30 PM **Board Discussion**

Charge to the Board:

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

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

3:00 PM **Break**

3:15 PM **OPP Presentation: Revised Product Performance Test Guidelines for Insect Repellents to be Applied to Human Skin** – Mr. John Carley (OPP, EPA) and Mr. William Jordan (OPP, EPA), with Clara Fuentes, Ph.D. (OPP, EPA) and Mr. Kevin Sweeney (OPP, EPA)

3:45 PM **Board Questions of Clarification** – Sean Philpott, Ph.D. (HSRB Chair)

4:15 PM **OPP Presentation: Settlement Agreement in Litigation Against EPA's Human Studies Rule** – Mr. William Jordan (OPP, EPA)

4:45 PM **Board Questions of Clarification** – Sean Philpott, Ph.D. (HSRB Chair)

5:15 PM **Preview of Upcoming Meetings** – Ms. Kelly Sherman (OPP, EPA)

5:20 PM **Adjournment**

* Agenda times are approximate and subject to change. For further information, please contact the Designated Federal Officer for this meeting, Jim Downing, via telephone: (202) 564-2468 or e-mail: downing.jim@epa.gov.

HSRB WEB SITE: http://www.epa.gov/osa/hsrb/
Docket Telephone: (202) 566-1752
Docket Number: EPA-HQ-ORD-2010-0381