October 30, 2009

Minutes of the
United States Environmental Protection Agency (EPA)
Human Studies Review Board (HSRB)
October 20-21, 2009 Public Meeting
Docket Number: EPA-HQ-ORD-2009-0658
HSRB Web Site: http://www.epa.gov/osa/hsrb

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

Date and Time:	Tuesday, October 20, 2009, 10:30 AM – 6:00 PM Wednesday, October 21, 2009, 8:30 AM – 1:00 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:	Suzanne C. Fitzpatrick, Ph.D., D.A.B.T. 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 Lois D. Lehman-McKeeman, Ph.D. Jerry A. Menikoff, M.D. Rebecca Parkin, Ph.D., MPH William J. Popendorf, 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

Dr. Paul Lewis (Designated Federal Officer [DFO], Human Studies Review Board [HSRB or Board], Office of the Science Advisor [OSA], U.S. Environmental Protection Agency [EPA or Agency]) welcomed Board members and the public to the meeting. He thanked his colleagues in EPA's Office of Pesticide Programs (OPP) for their work preparing for the

meeting. Dr. Lewis introduced Dr. Sean Philpott as the new Chair of the HSRB and Dr. Janice Chambers, who has agreed to serve as Vice Chair. He thanked Dr. Rebecca Parkin for serving as Interim Vice Chair. Dr. Lewis introduced three new members of the HSRB:

- Dr. Vanessa Northington Gamble is University Professor of Medical Humanities at George Washington University and an expert in the history of American medicine, racial and ethnic disparities in health and health care, and bioethics.
- Dr. Sidney Green is an Associate Professor of Pharmacology at the Howard University College of Medicine and has extensive experience in toxicology.
- Dr. William J. Popendorf is a Professor of Industrial Hygiene at Utah State University and has developed predictive models describing how worker exposure to hazardous substances can be controlled.

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

According to FACA requirements, meeting minutes (including descriptions of the discussions and conclusions reached by the Board) will be prepared. These minutes will be certified by the chair within 90 days of the meeting and posted at www.regulations.gov and on the HSRB Web site. Board members will also prepare a report; completion and approval of this report will be announced in the *Federal Register.*

Introduction and Identification of Board Members

Dr. Philpott welcomed Board members, EPA staff, and members of the public to the October 20-21, 2009 HSRB meeting. He acknowledged the efforts of Dr. Lewis, Board members, and EPA OPP staff in planning and preparing for this meeting.

Welcoming Remarks

Dr. Warren Lux (Director, Program in Human Research Ethics, OSA, EPA) welcomed Board members, EPA staff, and members of the public to the meeting. He expressed thanks from Dr. Kevin Teichman (Acting Science Advisor, OSA, EPA), who was unable to attend the meeting. He recognized the work of Dr. Lewis in establishing the HSRB and planning and conducting HSRB meetings and thanked him for his service to the Board. Dr. Lewis has accepted a position with the National Institutes of Health, which will begin in December 2009. Dr. Lux thanked Drs. Philpott and Chambers for serving as Chair and Vice Chair of the HSRB and welcomed new Board members to the meeting.

Opening Remarks

Mr. Steve Owens (Assistant Administrator, Office of Prevention, Pesticides, and Toxic Substances [OPPTS], EPA) thanked the Board members for their efforts in preparing for this meeting and for their thoughtful discussion and review of issues brought before them at this and previous meetings. He noted that Ms. Lisa Jackson (EPA Administrator) has articulated that EPA's work should be guided by transparency, sound science, and the rule of the law. The Board's efforts will help EPA meet these standards.

EPA Follow-up on Pesticide Specific HSRB Recommendations

Mr. William Jordan (OPP, EPA) thanked the Board for their efforts and also expressed thanks from Dr. Debbie Edwards (Director, OPP, OPPTS, EPA), who was unable to attend the meeting. He thanked Dr. Lewis for his service to the Board. The Board was created in response to a regulation requiring appropriate protection for participants involved in human research. The studies reviewed by the Board often must be reviewed quickly, as the study results are critical to EPA regulatory decisions. Dr. Lewis was instrumental in managing the process that created the Board and ensuring its productivity and constructive advice through establishment of Board standard operating procedures (SOPs).

Mr. Jordan informed the Board that additional information had been received from Dow Agro Sciences regarding previously conducted chlorpyrifos studies that had been reviewed at the June 2009 Board meeting. At that meeting, the Board reviewed a study performed at MDS Harris by Kisicki et al. EPA has received a letter from Dr. Kisicki and has reviewed this letter to develop a supplemental ethics review of the study. This will be provided to the Board for consideration in their report. In response to questions arising during EPA's ethics review, Dow Agro Sciences submitted additional documentation from MDS Harris on October 5, 2009. These documents are currently undergoing EPA review. The Agency plans to consider this information along with the Board's final report from the June 2009 meeting as it finalizes its ethics review of the study. At this point, EPA does not plan to bring the study to the Board for additional review.

Dow Agro Sciences also submitted additional information addressing scientific concerns that arose during the June 2009 HSRB meeting. On July 24, 2009, Dow Agro Sciences submitted a document in response to EPA's query regarding chemical and statistical analyses in the chlorpyrifos study. They provided additional information on 3,5,6-trichloro-2-pyridinol (TCP) hydrolysis and analysis, justification for the differences in absorption observed in different volunteers, and more thorough descriptions of the analytical methods used and reported in the Kisicki et al. manuscript. These documents are currently undergoing review at EPA; the Agency will consider these documents and the Board's report for its final science review. The Agency does not plan to bring this study to the Board for additional review.

EPA has been working to revise its guidelines for evaluating the efficacy of skin-applied insect repellents. An improved draft has been completed, but the final document is not yet complete. Recently, the World Health Organization (WHO) issued guidelines for evaluating such products and the Agency is reviewing these guidelines, as EPA strives to be consistent with

WHO recommendations. EPA plans to release its guidelines to the public before the end of 2009.

Dr. Linda Young commented that the Board faces continuing challenges in reviewing the scientific validity of studies that rely on antiquated guidelines, particularly regarding statistical analyses. She emphasized that solid statistical guidance must be included in EPA's guidelines.

Published Reports of Pyrethrins/Pyrethroids Research Completed Before Enactment of EPA's Expanded Human Studies Rule (40 Code of Federal Regulations (CFR) part 26: Protection of Human Subjects)

Background and Context

Ms. Sarah Winfield (OPP, EPA) introduced the two pre-Rule studies of pyrethrins/pyrethroids that EPA wishes to add to the body of evidence considered in its 2009 analysis of the relationship between pyrethrins/pyrethroids exposure and asthma and allergies. Crude pyrethrum is derived from the chrysanthemum flower, has insecticidal properties and is a known allergen. Pyrethrins are derived from refined pyrethrum; pyrethrins comprise six insecticidally active isomers and are regulated as one active ingredient. Synthetic pyrethroids were developed to modify the structure of natural pyrethrins to increase photo-stability and enhance insecticidal activity. Each pyrethroid is regulated as a distinct insecticide active ingredient.

Allegations of risk of asthma/allergies from exposure to pyrethrins/pyrethroids have been made by the Center for Public Integrity and in public comments received by the Agency. Previous EPA risk mitigation decisions led to a phase-out of organophosphates from the indoor residential market, which led to an increase in use of pyrethrin/pyrethroid products. In July 2008, EPA received correspondence indicating an increased incidence in allergies/asthma; considering that pyrethrum is a known allergen, it is not surprising that increased use of pyrethrum-derived products could increase allergy incidence.

EPA's new Registration Review program replaces its Re-Registration program; the new program will review all pesticides every 15 years to determine whether they continue to meet Agency standards for registration. Previous reviews of these substances include an EPA Office of Radiation and Indoor Air review of indoor air asthma triggers that determined evidence was inadequate or insufficient to conclude whether or not an association exists. The review also acknowledges that use of pesticides might decrease allergies by eliminating dust mites and cockroaches from indoor environments. In 2003, the Food and Drug Administration labeled its over-the-counter lice-control products that contained pyrethrins/pyrethroids to include a statement advising users with allergies to ragweed to consult a physician before use of the products, which could cause breathing difficulty or an asthma attack. EPA OPP's Re-Registration Eligibility Decisions (2006) considered label warnings, but ultimately decided that the evidence was not strong enough. Instead, language was included on labels indicating that adults, children, or pets should not enter an area treated with pyrethrins/pyrethroids until vapors, mists, and aerosols have dispersed and the treated area was thoroughly ventilated.

EPA has developed a white paper, "A Review of the Relationship between Pyrethrins, Pyrethroid Exposure and Asthma and Allergies" that integrates animal, human incident, and epidemiological information. The Agency has found no clear and consistent pattern of effects that would conclusively indicate an association between pyrethrins/pyrethroids exposure and asthma and allergies; however, human studies involving intentional exposure were not included in this analysis. Therefore, EPA proposes to add the following studies to the body of evidence considered in the 2009 analysis: (1) Newton, J.; Breslin, A. (1983) Asthmatic reactions to a commonly used aerosol insect killer. *Medical Journal of Australia* 1:378-380; and (2) Lisi, P. (1992) Short Communication: Sensitization risk of pyrethroid insecticides. *Contact Dermatitis* 26:349-350. These are intentional exposure studies that may provide direct information on the relationship between pyrethrins/pyrethroids and allergies and asthma, but the studies themselves have significant limitations. EPA attempted to contact the authors to obtain additional information, but was unsuccessful. The Agency's review of the manuscripts thus was based only on the published information.

Clarifying Questions

Dr. Michael Lebowitz stated that EPA's white paper was useful, but incomplete. He noted serious limitations to the animal studies cited; few true animal models of allergies or contact dermatitis exist. An agricultural health study that might have yielded useful information was not cited. He advised EPA to expand this document to include additional analyses.
Dr. Lois Lehman-McKeeman asked how EPA used in its white paper data from an unpublished master's thesis that provides evidence of a correlation between pyrethrins/pyrethroids and allergies. Ms. Winfield explained that EPA's review did not directly use the thesis; the thesis was utilized in a previous Agency review. This prior review provided the data included in the weight of evidence (WOE) as a secondary source. The data EPA relied on was poison control center data rather than data from an intentional exposure study.

EPA Science Assessment: Newton & Breslin Study (1983)

Ms. Carol Christensen (OPP, EPA) provided the Agency's science review of the Newton and Breslin study. This was a hospital-based, intentional exposure study conducted in the Chest Unit of Concord Hospital in Concord, New South Wales, Australia. The objectives of the study were to analyze the response of asthmatics to pyrethrin and tetramethrin contained in insecticide end-use products; study the time course of exacerbation of asthma following insecticide exposure; and characterize a potential mechanism of asthmatic reaction (immune response versus local irritant effect). Participants in the study were between 18 and 75 years of age; had well-controlled, mild, or moderate asthma; had previously self-reported chest tightness upon exposure to aerosol fly-killer insecticide; and were not pregnant and did not report a history of cardiovascular disease. The test substance was an aerosol insecticide containing pyrethrins and tetramethrin and was well-characterized. Participants were exposed to the insecticide in an enclosed testing chamber. Although EPA cannot confirm this, participants appear to have been blinded to the specific insecticidal products (they were told they were exposed to one of several different insecticides) and the investigators were not blinded.

On the first day of testing, medical history and preliminary measurements of lung functions were obtained in response to histamine dosing. Testing with insecticide also took place, and consisted of 5 seconds of exposure, followed by 5 minutes in the chamber post-exposure. Lung function measurements were repeated upon immediate exit from the chamber. If no asthmatic reaction was observed, participants were asked to return to the testing chamber for an additional 10-, 20- or 30-second exposure duration. Testing was ceased if evidence of an asthmatic response was observed. After the last exposure interval, participants were observed for 3 hours for signs of an asthmatic response and then were permitted to leave the test site. Day 2 of testing commenced with a repeat of the histamine challenge, which the investigators attempted to perform as close to exactly 24 hours after the participants' initial exposure to the test substance. All participants also were exposed to placebo (water) to determine if stress due to the testing regimen (e.g., being in the enclosed testing chamber) was responsible for any respiratory effects observed. On Day 3, one subject (Table 1, #1) who had evidence of a significant change in lung function (forced expiratory volume in 1 second [FEV_1]) was administered a bronchodilator before insecticide exposure. After 16 minutes, the participant was exposed to insecticide using the same regimen as on Day 1. This testing was conducted to determine if the response could be repeated.

No formal statistical analysis of the results was performed; instead, simple counts and proportions were provided. The 7 participants selected for the study were between 24 and 71 years of age and included 5 women and 2 men. Asthmatic response had been self reported by all 7 participants. No significant changes in histamine response after provocation with insecticide were observed; however, this was measured in only 4 of the 7 participants. Three of the 7 participants showed evidence of airway narrowing, and 1 of the 7 showed a significant fall in FEV_1 (approximately 35 percent) on Days 1 and 3. The authors concluded that although all participants self reported an asthma-like response, little quantitative evidence of asthmatic response was generated. Only 1 participant showed a change in lung function (FEV_1) and 3 had evidence of slight airway narrowing. The authors stated that further work was needed to determine a mechanism of the reaction and to clarify the component(s) of the end-use product responsible for the reaction.

Study limitations include the inconsistency between self-reported asthmatic reactions by all participants and quantitative change in lung function observed in only one participant. The authors acknowledged that the asthmatic response observed after use of the bronchodilator was unexpected. The study sample size also is small and likely does not capture variability in the population. Variables such as smoking, occupation history, and age were not directly addressed in the study. The time during which the study was performed (1983) suggests that outdated methods were used and casts doubt on the accuracy and precision of the measurement of lung function.

Assuming the performance of the study did not deviate from the published report, EPA has concluded that the data appear to be scientifically valid. The Agency considers it appropriate to use the data in a qualitative WOE consideration, but the data are not appropriate to be used for quantitative risk assessment.

Clarifying Questions

In response to a question from Dr. Dallas Johnson, Ms. Christensen clarified that only one subject underwent exposure on Day 3 of the study. Dr. Parkin asked if the study was conducted at the hospital with which the authors were affiliated. Ms. Christensen answered that EPA assumes this was the case, although they do not have direct information to confirm this. Dr. Parkin inquired if EPA had any additional information on the test chamber. Ms. Christensen responded that EPA attempted to contact the study authors, but were unable to obtain additional information on the test chamber or other matters.

Dr. Lehman-McKeeman asked if the subjects all reported chest tightness after the 5- and 10- second exposures. Ms. Christensen confirmed that they had. Dr. Lehman-McKeeman questioned if testing ceased if the patient showed a decrease in FEV_1 or if they reported chest tightness. Ms. Christensen explained that how the decision to proceed was made was unclear. Dr. Lehman-McKeeman inquired if EPA's statement that participants were exposed to approximately 6.7 milligrams (mg) per liter (L) was calculated or based on measurements. Ms. Christensen replied that the exposure level was calculated based on insecticide can weight reported before and after use and the area of the chamber. Neither passive dosimetry nor other methods were used to directly measure the level of insecticide.

Dr. Young inquired if the authors used the term "correlation" in a statistical sense, in the context of the reported relationship between symptoms and quantitative measures of lung function. Ms. Christensen explained that EPA's report noted the inconsistencies between FEV_1 measurements and reported symptoms and agreed that neither the study authors nor the Agency used the term "correlation" in a strict statistical sense; the term was used qualitatively rather than quantitatively.

Dr. Lebowitz questioned if EPA had reviewed the 2009 American Thoracic Society/European Respiratory Society standards on asthma and lung function. Ms. Christensen responded that EPA had not reviewed these standards. Dr. Parkin requested clarification regarding the number of participants who were tested on Day 2. Ms. Christensen explained that all 7 participants returned to the test site on Day 2 to participate in the placebo evaluation. Only 4 of the 7 participated in the histamine challenge on Day 2, and it is unclear why all did not participate. In response to a question from Dr. Johnson, Ms. Christensen clarified that the report did not indicate whether participants were able to distinguish between exposure to the insecticide and exposure to the placebo.

EPA Science Assessment: Lisi Study (1992)

Ms. Christensen presented EPA's science assessment of the Lisi study, which was a brief communication published in *Contact Dermatitis*. The study's author was affiliated with the Institute of Clinical Dermatology, University of Perugia, Perugia, Italy. The study objectives were to establish the irritation and sensitization potential of pyrethroid end-use products among members of a sensitive sub-group (i.e., people with pre-existing dermatological conditions (both allergic and non-allergic)). Seven pyrethroids were tested: allethrin, cypermethrin, deltamethrin, fenothrin, fenvalerate, permethrin, and resmethrin.

The author conducted patch tests using 3 different concentrations (1 percent, 2 percent, and 5 percent) of the test substances, applied to the upper back for each pesticide for each participant. The test substances were not well characterized in the report. The patches were read at 2 and 3 days post application.

No formal statistical analyses of the results were performed; instead, simple counts were provided in the tables. The study included 230 participants (162 men and 68 women) between 19 and 78 years of age. The authors categorized the participants as agricultural workers (82), former agricultural workers (28), and others (120) based on assumptions regarding potential prior exposure to the test substances. Among the 230 participants, 5 cases of irritation and/or allergic reaction were observed. Two irritant reactions to resmethrin were observed in non-atopic participants. One allergic reaction to cypermethrin was observed, but the author stated that this reaction was "not clinically relevant"; no additional detail was provided. Two allergic reactions to fenvalerate were observed. Both participants with evidence of this reaction had chronic dermatitis of the hands. One of these participants had previously observed sensitization to non-pyrethroids and the other was a gardening hobbyist, which implies possible exposure to pesticides. The author concluded that pyrethroids are only very slight cutaneous irritants or sensitizers.

Study limitations noted by EPA include a lack of information concerning the purpose for evaluating the effects of these substances among persons with pre-existing skin conditions. No background information was provided regarding these pre-existing conditions and the study population was not well characterized. The selection criteria were not defined, and thus it is difficult to determine to which sub-groups these results could be applied. The purpose of classifying participants in three sub-groups was not specified. The agricultural worker versus non-worker groups presumably differed in their prior exposure to pyrethroids, but a description of the "other" group was not provided. Details about other pesticide exposure were not provided.

Regarding the study itself, actual dosages used were not identified. Perhaps most importantly, outcome definitions (e.g., sensitization versus irritation) were not provided. The protocol used to differentiate between irritant and sensitization effects was not specified. Adherence to the protocol by the participants (i.e., whether the test patches remained in place for 3 days) also was not described.

The Agency has concluded that this study suggests that there is little evidence of irritation or sensitization effects of pyrethroids among people with various (unspecified) pre-existing dermatological conditions. Given the study limitations, EPA considers the data to be minimally adequate for inclusion in a qualitative WOE.

Clarifying Questions

Dr. Parkin inquired about the International Contact Dermatitis Research Group (ICDRG) criteria referenced in the article regarding the patch test protocol. Ms. Christensen stated that EPA had not obtained these criteria but offered to do so. Dr. Parkin noted that these criteria

could clarify questions regarding how the reactions were read. Dr. Johnson asked if each participant received all three doses of all seven pyrethroids simultaneously. Ms. Christensen responded that while it appeared that this was the case, it was potentially a single patch with numerous compartments within the patch.

EPA Ethics Assessment: Newton and Breslin Study (1983)

Ms. Kelly Sherman (OPP, EPA) provided EPA's ethics assessment of the Newton and Breslin study, which evaluated asthmatic subjects for airway narrowing and chest tightening following exposure to an aerosol pyrethrin spray. The results of this study contribute to the WOE regarding a potential relationship between exposure to pesticides containing pyrethrins or pyrethroids and asthmatic or allergic responses.

The participants included in this study were 2 men and 5 women between 24 and 71 years of age. The participants had a history of proven bronchial asthma and of chest tightness upon exposure to aerosol insecticides. The participants were stated to be not "pregnant or liable to be pregnant" and did not have cardiac disease. Information on how the participants were recruited was not available.

Risks to the participants were not discussed in the article. There was an unaddressed risk of significant respiratory reaction to the test substance. Risk minimization measures included plans to stop the challenge in the event of a significant asthmatic reaction, follow up for 3 hours after the challenge ("most" patients), and asking the participants to report any asthmatic reaction developing during the 24 hours following exposure to the pesticide. Benefits were not discussed in the article, and no direct benefits to participants existed. Potential societal benefits were limited by the small sample size and other design issues, but the study could potentially contribute to the body of knowledge about pyrethrin insecticides. EPA cannot discern whether the investigators assessed the risk:benefit balance prior to conducting the research. The perceived limited benefit of the information gained from this study might not have outweighed the small, but non-zero, risk of a catastrophic outcome.

No ethics oversight was reported, but the authors did report that informed written consent was obtained before the trial began. No further details about consent were provided. EPA determined the applicable standards of the time to be the Declaration of Helsinki (DoH) (1975); standards of acceptability are 40 CFR §26.1703 and 40 CFR §26.1704. Based on the authors' statement concerning informed consent, the research was consensual and not intended to harm the participants. No information was available to assess whether the research was conducted consistent with the three basic principles of the DoH, namely independent ethical review, prior assessment of risks and benefits, and a favorable risk:benefit balance; however, there is no evidence that the research was not conducted consistent with these principles. The tenets of 40 CFR §26.1703 and 40 CFR §26.1704 appear to have been met, namely that no intentional exposure of pregnant or nursing women or of children occurred and there also is no clear and convincing evidence that the research was fundamentally unethical or that the conduct was significantly deficient relative to prevailing standards. The Agency has concluded that if the research is deemed scientifically valid and relevant, there are no barriers in the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) or in 40 CFR §26.1703 or 40 CFR

§26.1704 to prevent EPA's reliance on the Newton and Breslin study in actions taken under FIFRA or §408 of the Federal Food, Drug and Cosmetic Act (FFDCA).

Clarifying Questions

The Board did not ask clarifying questions for the ethics assessment of the Newton and Breslin study.

EPA Ethics Assessment: Lisi Study (1992)

Ms. Sherman presented EPA's ethics assessment of the Lisi study, which tested the dermal irritation and sensitization potential of seven pyrethroids. The data contributes to the WOE concerning a potential relationship between exposure to pesticides containing pyrethroids and dermal irritation or sensitization responses.

The study enrolled 230 subjects (162 men and 68 women) between 19 and 78 years of age. All participants were patients at the dermatological clinic where the research was conducted. The participants were classified as current agricultural workers (82), former agricultural workers (28), or other (120). Fifty-four of the subjects had been admitted or treated for irritant or allergic contact dermatitis of the hands and the remaining 176 had been admitted for non-allergic skin disorders.

The author did not provide information about recruitment. There was no evidence suggesting that any participants were from an especially vulnerable group, and no evidence that the subjects were coerced or otherwise improperly influenced to participate. Risks (e.g., risk of reaction to the test compounds) were not discussed with the participants. Benefits also were not discussed in the manuscript and the research appears to pose no direct benefits to the participants. The results of the research could be of potential societal benefit. No information was given to assess whether the investigators assessed the risk:benefit balance before conducting the research. The potential value of the research is perceived to outweigh the risks to the participants.

Ethics oversight was not reported. The article also does not mention "informed consent" but the subjects are referred to as "volunteers." The applicable standard of conduct is the DoH (1989) and the applicable standards of acceptability are 40 CFR §26.1703 and 40 CFR §26.1704, although the author does not assert this in the article. Regarding compliance with standards of conduct, the research was apparently consensual and not intended to harm the participants. Information to assess whether the conduct was consistent with two of the basic principles in the DoH (independent ethics oversight and prior consideration of a risk:benefit balance) was not available; however, there is no evidence that the research was conducted inconsistent with these principles.

The research appears to have been conducted in accord with the requirements of 40 CFR §26.1703 and 40 CFR §26.1704, namely that no intentional exposure of pregnant or nursing women or of children occurred and there also is no clear and convincing evidence that the research was fundamentally unethical or that its conduct was significantly deficient relative to

prevailing standards. The Agency has concluded that if the research is deemed scientifically valid and relevant, there are no barriers in FIFRA or in 40 CFR §26.1703 or 40 CFR §26.1704 to prevent EPA's reliance on the Lisi study in actions taken under FIFRA or §408 of FFDCA.

Clarifying Questions

Dr. Northington Gamble requested clarification regarding EPA's definition of "vulnerable" populations. The Lisi study may have included migrant workers who might have been in vulnerable situations. She also asked EPA to clarify the phrase "especially vulnerable." Ms. Sherman explained that within an ethics review, "vulnerable" refers to whether the subject might be under undue influence or coercion to participate or are not adequately able to make a decision about participating. EPA does not automatically consider specific groups to be vulnerable, but does consider their vulnerability during the review. The documents associated with the Lisi study do not provide sufficient information to judge whether the participants were members of vulnerable groups. She added that there is no distinction between "especially vulnerable" and "vulnerable"; EPA does not consider degrees of vulnerability.

Mr. Jordan responded to previous questions regarding EPA's familiarity with official statements regarding asthma control and exacerbation. When the Agency decides to perform a risk assessment, such as is described in the white paper discussed at this meeting, multidisciplinary teams are established to perform the analysis. In this case, team members included inhalation toxicologists and members of other scientific disciplines. This team did consider statements from the American Thoracic Society regarding asthma in their development of the white paper.

Mr. Jordan explained that EPA developed and publicized the white paper because of concerns about the relationship between pyrethrin/pyrethroid products and allergies and asthma. The Agency has invited public comment on the white paper. In the course of its analysis, EPA recognized that some previously performed intentional dosing studies might contain relevant information and thus has asked that the Board review the studies. The data will be incorporated into the revised white paper based on the Board's conclusions regarding the acceptability of these studies.

Dr. Parkin inquired whether the "baseline" data from the Newton and Breslin study referred to average readings or the highest readings obtained. Ms. Christensen responded that this was unclear; EPA assumed that the measurements in table 1 referred to the amount of histamine needed to achieve a 20 percent reduction in FEV_1 on Day 1, before exposure to the insecticide. This measurement was repeated 24 hours post-exposure and FEV_1 was also determined when the participants left the chamber. Dr. Parkin clarified that she was referring to the "3 baseline readings" referenced on the second page of the article. Ms. Christensen explained that each reading was taken 3 times, but whether maximal or average readings were reported is unclear; typically, average values are used.

Public Comments

Mr. Stephen McFadden, Independent Scientific Research Advocates

Mr. McFadden described sensitive human subpopulations, several of whom are particularly sensitive to pesticides. For example, people with ornithine transarbamylase deficiency can develop cerebral edema if they are directly exposed to DEET. In addition, some people with differences or deficiencies in acetylcholinesterase metabolism might suffer ill effects if exposed to organophosphates or carbamate. Most studies that analyze sensitivity to insecticides involve too few people to include members of these sensitive subpopulations. Eventually, data from the Human Genome Project and computational toxicology research will help identify members of these sensitive subpopulations, but this is likely to take many years.

Pyrethroids present less risk than organophosphates and carbamate because they tend not have systemic effects, causing skin rashes or asthma as opposed to central nervous system reactions. Although the mechanism of action of pyrethroids is unknown, they are known to inhibit ion channels and sulfate metabolism and some people may be less able than others to detoxify pyrethroids.

Because all pesticides will be re-regulated, Mr. McFadden's group wished to express concern regarding the lack of information about the neurotoxicity of pesticides. For example, research has found that epilepsy can be induced by an initial seizure event, which can be triggered by certain drugs or other stimuli; this initial event may increase the likelihood of subsequent events. Exposure to cholinesterase inhibitors also may cause a seizure event. Mr. McFadden's group would prefer that organophosphates be banned from indoor use and aerial spraying. He acknowledged that pyrethrins are considered to be less toxic than organophosphates.

Dr. Green inquired if the sensitive subpopulations described by Mr. McFadden should be considered vulnerable populations. Mr. McFadden explained that they may be considered vulnerable for a number of reasons. He noted that these people may be considered somehow defective (i.e., being one in a million with a defect) by some, but that a large number of variant detoxification pathways exist and thus these problems may actually affect a large proportion of the population. In addition, some of these variations are evolutionarily adaptive; for example, although slower detoxification may result in toxicity effects, fast detoxification could activate a carcinogen.

Dr. Lawrence Plumlee, American Academy of Environmental Medicine

Dr. Plumlee stated that his group is concerned about protecting the rights of people for whom there is little benefit in evaluating the human toxicity of pesticides. Almost all people are exposed to pesticides on a regular basis; therefore, benefits can accrue to sensitive populations if work is performed before (or soon after) the pesticides are marketed to determine the proportion of the population sensitive to the pesticides, at what level effects are observed, and what degree of damage can be caused by exposure.

Pesticide tolerance levels are based on data from animal studies and safety factors; however, many people are sensitive to common pesticides even at recommended levels and how the pesticides are used after marketing is not explored systematically. For example, timed-release devices that aerosolize pyrethrins/pyrethroids to decrease mosquito populations are used indoors and, although legal to use in such a manner, their use may adversely affect some people. He asked that as EPA and the Board consider whether a study can be considered ethical, they consider the millions of people who are currently exposed to pesticides in the absence of solid data about the consequences of exposure. Increasing awareness of genetic variations that may affect response to exposure is important. He encouraged a liberal attitude toward developing and reviewing existing scientific studies to determine true risk. Pesticides have benefits, but risk must also be understood to realize the true impact of pesticide use on humans.

Charge Questions

The Board was asked to consider the following charge questions for the Newton and Breslin and the Lisi studies.

Newton and Breslin Study (1983):

1. Is the Newton and Breslin study scientifically sound, providing reliable data?
2. If so, is the Newton and Breslin study relevant to an assessment of the proposition that exposures to pyrethrins/pyrethroids may be associated with asthmatic or allergic respiratory responses?
3. If so, what limitations of the Newton and Breslin study should be taken into account by EPA in assessing the proposition that exposures to pyrethrins/pyrethroids may be associated with asthmatic or allergic respiratory responses?
4. Is there clear and convincing evidence that the conduct of the Newton and Breslin study was fundamentally unethical, or that its conduct was significantly deficient relative to standards prevailing when it was conducted?

Lisi Study (1992):

1. Is the Lisi study scientifically sound, providing reliable data?
2. If so, is the Lisi study relevant to an assessment of the proposition that exposures to pyrethrins/pyrethroids may be associated with allergic contact dermatitis or sensitization responses?
3. If so, what limitations of the Lisi study should be taken into account by EPA in assessing the proposition that exposures to pyrethrins/pyrethroids may be associated with allergic contact dermatitis or sensitization responses?
4. Is there clear and convincing evidence that the conduct of the Lisi study was fundamentally unethical, or significantly deficient relative to the standards of ethical research conduct prevailing when it was conducted?

Review and Discussion of HSRB Criteria for Consideration of Pre-Rule Human Dosing Studies

Dr. Philpott presented criteria developed by the Board for consideration of pre-Rule human dosing studies. At its May 2006 meeting, the HSRB established several points of consideration for scientific review of pre-Rule studies. These included justification, dose selection, endpoint selection, participant selection, methodology, and statistical analyses. Specifically, justification of the study must include consideration of whether the scientific question(s) asked are worthwhile, whether human participants are necessary to answer the question(s), and whether the potential risk to human participants is serious or irreversible. The Board also should consider whether the doses (in most cases single doses are insufficient) selected are adequate to answer the question(s) and based on appropriate data. The study must have an endpoint that is consistent with the aim of the analysis, is appropriate for answering questions about human responses (e.g., sensitivity, accuracy, validity, replicability), and must be able to be accurately and reliably measured. Participant selection must consider whether the characteristics of the participant population are appropriate and generalizable to the questions asked and whether appropriate inclusion and exclusion criteria were defined. The methodology should include sufficient sample size; selection of appropriate control and experimental groups; appropriate staging of dose intervals, dose amounts, and types of exposure; and quality assurance (QA) for observations, instruments, and data. It should be possible to statistically analyze the data and the statistical methods used must be appropriate for answering the research questions.

Dr. Philpott instructed the Board to consider the data from the Newton and Breslin and Lisi studies in the overall WOE, but to remember that EPA reviewed the studies from a qualitative perspective. Additionally, the Board has not been asked to comment on EPA's white paper on this topic.

Dr. Philpott acknowledged that reviewing the ethical conduct of pre-Rule studies can be challenging. The main standards for assessing whether EPA can rely on the results of human subject research include 40 CFR §26.1703, prohibition of reliance on research involving intentional exposure of human subjects who are pregnant women (and therefore their fetuses), nursing women, or children; 40 CFR §26.1704, which prohibits reliance on unethical human research with non-pregnant, non-nursing adults conducted before April 7, 2006; 40 CFR §26.1705, which prohibits reliance on unethical human research with non-pregnant, non-nursing adults conducted after April 7, 2006; and 40 CFR §26.1706, which describes criteria and procedures for decisions to protect public health by relying on otherwise unacceptable research. Beyond these regulations, the Board must determine that EPA cannot use the research if there is clear and convincing evidence that conduct of the research was fundamentally unethical or significantly deficient relative to the ethical standards prevailing at the time the research was performed. Examples of prevailing ethical standards include FIFRA Section 12(a)2(P), the DoH or other accepted Codes, and the Common Rule (40 CFR part 26). In the absence of clear and convincing evidence that the study was unethical or significantly ethically deficient, the assumption is that EPA can use the data; the onus is on the Board to prove that the research was unethical. "Fundamentally unethical" is described as research performed with intent to harm or a significant likelihood of harming the participants. Research can be judged significantly deficient if the risks of the research are judged too high or there were deficiencies in the informed consent

process severe enough to raise questions concerning whether participation was voluntary and informed.

Board Science Review: Newton and Breslin Study (1983)

Dr. Lehman-McKeeman opened the science discussion of the Newton and Breslin study by expressing significant reservations over the scientific validity of the results. The sample size was small (only 7 subjects) and descriptions of outcomes were incomplete and inadequate. Data for the histamine challenge for 3 of the subjects, 1 of whom appeared to have a response, was incomplete; therefore, the study technically has complete data for only 4 subjects, although the importance of the histamine challenge data is questionable. Dr. Lehman-McKeeman noted differences between the FEV_1 data presented in the table and the authors' description of it. The authors indicate that 3 baseline measures were taken, but only 1 value is given and it is unclear whether the value provided represents a minimum, maximum, or average value. No information is provided to determine if the measurements fall into the normal range; population data cannot be used to determine this because information on the participants' health and other variables was not provided. Based on the way the data are discussed, the decrease in FEV_1 values reported in table 1 could be assumed to represent the maximum change in this value, but this cannot be confirmed. Thus, it is difficult to determine the meaning of the FEV_1 values for this study. In addition, a measured FEV_1 value is provided for Participant #4, but no maximum mid-expiratory flow rate (MMEFR) value is provided for this participant.

Dr. Lehman-McKeeman summarized that the data are inadequate and incomplete; therefore, it is difficult to assess whether or not the science is valid. She stated that she could not conclude the data are scientifically valid because of their incompleteness. The authors note that all participants experienced chest tightness and other symptoms; this would seem to indicate significant irritation, although perhaps not an allergy, and may have influenced the respiratory measurements taken. Therefore, the Newton and Breslin study is unlikely to provide scientifically sound, reliable data.

Regarding the relevance of the Newton and Breslin study for testing the relationship between pyrethrin/pyrethroid exposure and asthmatic or allergic respiratory responses, the test material was well characterized, but contained other ingredients; therefore, the data are specifically relevant only to the test formulation and may not be generally applicable to pyrethrins/pyrethroids. One ingredient in this formulation was piperonyl butoxide, which has a known relationship to allergies and asthma and this is present in higher concentrations than pyrethrin; therefore, the data from the Newton and Breslin study is unlikely to be relevant to an assessment of the relationship between pyrethrin/pyrethroid exposure and asthma or allergies and is instead relevant only to the particular product tested.

Regarding limitations of the study, Dr. Lehman-McKeeman concluded that these were too numerous for EPA to consider the data from the study to be scientifically valid, reliable, and informative for the question asked.

Dr. Chambers agreed with Dr. Lehman-McKeeman's assessment of the Newton and Breslin study. The study tested a formulation containing a number of different components and

thus it is not possible to conclude that only the pyrethrins/pyrethroids had an effect. No controls for solvent or vehicle were included. Use of a bronchodilator by one subject also may have confounded the data. She concluded that there are too many limitations to the data and the effects cannot be specifically attributed to pyrethrins/pyrethroids. Thus the data are not scientifically reliable.

Dr. Young agreed with her colleagues' assessments. She also noted that statistical terms were not properly used in the manuscript. For example, the terms "correlation" and "significance" have specific meanings in the context of statistical analyses.

Dr. Lebowitz opened his science review of the Newton and Breslin study by noting that the study was conducted in a clinic housed in a teaching hospital, used a reasonably well-characterized population of patients (although only with respect to asthma and respiratory issues), and used commonly accepted hypersensitivity measures defined by various groups who work on respiratory diseases. In 1971, standards for lung function testing called for taking 3 measurements, and then reporting the maximum value of the best measurement; therefore, the baseline FEV_1 reported in the document is likely the maximum of the 3 measurements. The protocol was reasonable and appropriate for the time it was performed. Histamine is used today to determine baseline for non-specific bronchial hyperactivity. The use of a placebo challenge indicates that non-generalized reactivity occurred.

Weaknesses to the study include a lack of blinding; knowing they were being exposed to pesticide may have produced a subjective response in the participants. Additionally, characterization of the patients was not thorough. Based on the baseline FEV_1 of 1.0, Patient #1 would currently not qualify for a histamine challenge test. The FEV_1 values for some of the other participants also seem low, although this is difficult to judge because data on age, height, gender, and race were not provided. MMEFR measurements were not performed for two of the reactive subjects; however, MMEFR responded substantially in 3 of the participants. This measurement was not reported for Patient #4 and it is unclear whether the measurement was not readable or could not be calculated. The authors also waited too long after exposure to the pesticide to perform the histamine challenge. Information on normally used medications and dermal irritation also would have helped define any pre-existing conditions the participants may have had. Using a larger dose of atropine to determine if it would block the irritant effect observed would have helped determine if the response was allergic in nature. Dr. Lebowitz agreed that the experiment did not specifically test pyrethrins but instead tested response to a specific product that contained pyrethrins/pyrethroids; however, he concluded that the study was scientifically sound, if limited, and the results were relevant to the assessment of the relationship between pyrethrins/pyrethroids and asthma or allergies.

Dr. Parkin commented on issues related to the test chamber. The authors did not provide a description of the protocols used for setting up the chamber, introducing the pesticide, and cleaning the chamber between subjects. She also raised questions about whether an exhaust fan in the chamber removed all fumes between sprays, which would impact the actual exposure. She noted that the documentation regarding which participants were exposed for 5, 10, 20, or 30 seconds was incomplete and unclear. The testing protocol also was unclear; for example, it appears that some participants may have withdrawn from the study before completion, although

this is unclear. Symptoms also could not be matched to participants. Using self-report data also is problematic, because some participants may have labeled their symptoms differently than others. Dr. Parkin concluded that EPA should not rely on these data.

Dr. Johnson agreed with Dr. Lehman-McKeeman's comments regarding the validity and reliability of the data from the Newton and Breslin study. Regarding the relationship between pyrethrins/pyrethroids and asthma or allergies, the data suggests an association, but is not sufficient to determine the existence of a relationship. He expressed some surprise that better studies on this subject could not be found by EPA.

Dr. Lebowitz agreed that the lack of follow-up testing on specific components in the test formulation was a significant limitation to the study; however, bronchial hyperactivity in response to exposure to the product occurred. He explained that he had considered his own knowledge of the technical details of pulmonary function testing when developing his analysis of the science of the study, which may have led to the difference in his opinion compared to other reviewers. He agreed that the data are relevant only to the product tested, but concluded that the data could nonetheless be useful in EPA's WOE assessment. Dr. Lebowitz stated that in his opinion, the data from this study do not differ greatly in quality from quantitative data from other human exposure studies that have been used by EPA for developing no observable adverse effects levels (NOAELs) and other measures. Given the lack of information in the relationship between pyrethrins/pyrethroids and allergies and asthma, the study is relevant. The questions about the chamber are not significant enough to conclude that the data are scientifically invalid.

Dr. Popendorf commented that the study lacked details on the chamber exhaust system and whether it was sufficient to prevent accumulation of the product. In addition, the poor calculations and incomplete information on dose and time of exposure raise questions about the data. Dr. Parkin noted that the chamber did have an exhaust fan, but no information regarding cleaning of the chamber was provided.

Dr. Philpott summarized that the Board had identified many limitations to the study, among them the lack of data for all participants, lack of information on chamber size and ventilation, and questionable exposure calculations. Regarding the second charge question, the Board had concerns that the responses observed may not be specifically attributable to pyrethrins/pyrethroids in the spray but rather to other components in the product. Regarding the validity and reliability of the data, a majority of Board members believe that the data cannot be judged scientifically sound because of the many limitations they identified, but Dr. Lebowitz believes that the data could be valid. Dr. Lebowitz clarified that if the data can be reproduced, they are reliable. The study is not sufficient in itself to provide quantitative data, but its accuracy and reliability should be sufficient for EPA's WOE. Dr. Philpott suggested that the Board could advise that the data could perhaps be used for a qualitative WOE. Mr. Jordan acknowledged that the study had limitations, but may be somewhat informative regarding the relationship between pyrethrins/pyrethroids and asthma. He noted that the Board's response to the second and third charge questions confirmed EPA's concerns and accepted the Board's decision that the data might be usable in a qualitative WOE.

Dr. Lebowitz stated that uncertainties about the response of participants to the product could be due to a lack of knowledge about lung function testing on the part of both Board members and EPA. EPA's review was not sufficiently knowledgeable to stand on its own. He agreed in general with the Board's conclusions, but advised that EPA reconsider its own review of the study in the context of existing standards of the time, which would help EPA determine if the data are acceptable or unacceptable. Dr. Philpott acknowledged Dr. Lebowitz's concerns and suggested that he relay them to EPA separately, as these concerns may be more applicable to the white paper than to the scientific review of the Newton and Breslin study. He summarized that the Board had concerns about the validity of the study; however, EPA may be able to use the data as qualitative information in a WOE review, but should be aware of the limitations on the data when doing so.

Board Ethics Review: Newton and Breslin Study (1983)

Dr. Philpott provided Dr. Jerry Menikoff's ethics review of the Newton and Breslin study. Dr. Menikoff agreed with EPA's ethics review regarding the conduct of this study. In accord with Board procedures for assessing the ethics of completed studies, there must be clear and convincing evidence that the study was conducted in an unethical manner or was significantly deficient with regard to ethics. The relevant standard EPA used to judge the ethics of this study was the DoH (1975). Given that the study was performed in Australia, which at the time was at the forefront of human subject protection, subjects were likely to be adequately protected. Dr. Menikoff raised concerns about the paucity of information provided in the study, particularly concerning the nature of the subject population and the informed consent process; however, in the absence of data to the contrary, the Board must conclude that EPA can use the data from this study if it is deemed scientifically sound.

Dr. Northington Gamble agreed with Dr. Menikoff's review. She questioned how EPA and the Board identify the prevailing ethical standard for a given study. She also asked if the Board considered whether a country was a signatory to the DoH and whether the standards for that country at that time were addressed. She reiterated her agreement with Dr. Menikoff's assessment, but commented that more context should be provided in the Board's ethics reviews of existing studies. Dr. Philpott noted that relative to the United States at the time, Australia had stricter human subject protection rules; therefore, if the investigators adhered to the prevailing Australian standards the study was likely conducted appropriately. He summarized that the Board found no clear and convincing evidence that the Newton and Breslin study was fundamentally unethical.

Board Science Review: Lisi Study (1992)

Dr. Lehman-McKeeman opened the science review of the Lisi study by commenting on its brevity, meaning that many details about the work were not provided. She suggested that the Board assume that the guidelines (ICDGR criteria) cited by the authors were met. The lack of details raises questions about the methodological execution of the study. Details about the dosages used were not available, nor was confirmation that the indicated dosages were applied. The study also lacked information concerning how an allergic reaction was distinguished from a hypersensitivity reaction. The study was performed for hazard identification, and thus there is

less concern about the lack of quantitative data for the response; however, there also is no information regarding the criteria used to designate the severity of the response; "irritation" could indicate redness or ulceration. Additional descriptions of the responses observed would have added validity to the study. The study also lacked information on participant compliance. It is unclear whether a negative control (vehicle) was used or if a positive control was used to judge the general responsiveness of the participants. Dr. Lehman-McKeeman summarized that she would tentatively conclude that the study provides scientifically reliable data. The data also are informative to assess the effects of exposure to pyrethrins/pyrethroids, given the limitations of the study.

Dr. Suzanne Fitzpatrick agreed with Dr. Lehman-McKeeman's assessment. She noted that if ICDRG criteria are commonly used as guidance for such studies, this would increase her confidence in the results. She agreed that the study lacked information regarding inclusion/exclusion criteria, past exposures, adherence to the protocol, details of the protocol (21 patches on each person versus 7 compounds at only 1 dose), and criteria for grading responses. Ms. Christensen clarified that ICDRG guidelines provide criteria used by dermatologists to read the results of the patch test. Regarding the number of patches applied to each participant, EPA believes that this could have been done by using 1 patch that had separate compartments for each product.

Dr. Young noted that no statistical analyses were performed for this study. Dr. Popendorf agreed, but commented that the response rate of 1 in 100 people was of questionable reliability. If the compounds were known sensitizers, a response rate of 10 to 20 percent could have been expected. The authors agree with this, as shown by their conclusion that pyrethrins/pyrethroids appear to be only slight irritants or sensitizers. Regarding the association of the products with irritation/sensitization, Dr. Popendorf noted that the 2 chemicals associated with a reaction were members of the cyano group of pyrethrins, suggesting that these may differ from other types of pyrethrins. He explained that the ICDRG provides 4 categories of response and thus the authors could have provided a more detailed description of the responses they observed and at what dose the responses occurred. He concluded that there is a low probability that the data would be useful.

Dr. Parkin agreed with most of the comments made by other Board members. She highlighted a footnote to table 1 that indicated allergic reactions occurred at all 3 doses and irritation occurred for the 5-percent dose. She stated that the lack of documentation raised many questions; the study was not highly informative and the response rate was low. She concluded that the study was not informative beyond providing qualitative information.

Dr. Philpott summarized that the study might be sound and does provide reliable data. The data are relevant to judging the relationship between pyrethrins/pyrethroids and allergic contact dermatitis and sensitization, although concerns were raised about the low response rate. Board members raised a number of concerns about limitations of the study related to its design and conduct. The Board concluded that EPA could rely on the study to provide some qualitative information on this issue.

Board Ethics Review: Lisi Study (1992)

Dr. Menikoff opened the ethics review of the Lisi study by stating that the study was relatively benign and there is no information indicating that it was performed with intent to harm the participants. Little information on the informed consent process was provided, but there was no indication that informed consent was not obtained. The report states that the subjects "volunteered" to participate. Given that the research was conducted in Italy, EPA is correct in assuming that the DoH is the relevant prevailing standard. Dr. Menikoff concluded that, in the absence of clear and convincing evidence that the study was fundamentally unethical or significantly deficient relative to standards for ethical research conduct prevailing at the time, EPA can rely on the data from this study.

Dr. Northington Gamble expressed some concern about relying solely on the DoH as the prevailing standard of the time. She noted that she had identified an article on medical ethics in Italy published in 1992 that described a new Italian code of research ethics. She advised EPA to more specifically consider the context of the research when determining which prevailing standards to apply. Dr. Northington Gamble questioned the identity of the patients; because this work was conducted at a dermatology clinic, there is a chance that some of the participants may have suffered from a venereal disease. She commented on the lack of information to determine whether the participants were members of vulnerable groups. Despite these deficiencies, Dr. Northington Gamble agreed that there was no clear and convincing evidence that the study was fundamentally unethical.

Dr. Philpott summarized that the research was not conducted in an unethical manner, with the caveat that little data was provided to judge this and that more clarity regarding prevailing ethical standards might be needed.

Proposed Antimicrobials Exposure Assessment Task Force (AEATF)-II Research on Exposure of Janitorial Workers Applying Antimicrobial Pesticides Formulated as Aerosol Sprays (Protocol AEA04)

Background and Context

Mr. John Carley (OPP, EPA) provided background on the proposed AEATF-II protocol, AEA04. AEATF-II submitted an Institutional Review Board (IRB)-approved scenario design and study protocol dated August 4, 2009, for an aerosol spray exposure study. The EPA science and ethics review dated September 21, 2009, reflects review of the August 4, 2009 proposal and was informed by the governing documents and SOPs developed by AEATF-II; the governing documents and SOPs have not been changed since the Board reviewed these documents in 2008.

AEA04 is a proposal for research involving scripted and thus intentional exposure of human subjects, with the intent to submit the resulting data to EPA under FIFRA; therefore, 40 CFR §26.1125 (which requires prior submission of the protocol and supporting documentation) and 40 CFR §26.1601 (which requires review of the protocol by EPA and the HSRB) apply to this proposed research. The August 4, 2009 submission by the AEATF-II contains all

elements required by 40 CFR §26.1125; therefore, EPA considers this proposal to be ready for HSRB review.

Mr. Carley provided background information on exposure monitoring. In the early 1990s, individual pesticide handler exposure studies were combined into a shared database, the Pesticide Handlers Exposure Database (PHED). "Handlers" were described as workers who mix, load, or apply pesticides. Data in the PHED has been used to support meta-analyses across studies, which demonstrates the value of determining exposure generically. PHED also has provided data used by EPA in its exposure assessments. Additional exposure monitoring specific to antimicrobials was conducted in a Chemical Manufacturers Association (CMA) study. The PHED and CMA data are the best data available, but have limitations, particularly for antimicrobials. Coverage of antimicrobial use patterns is incomplete and the studies had been conducted for different purposes; thus inconsistent methods increase the uncertainty of inferences drawn using the data.

EPA agrees that new exposure studies are needed to address the limitations of PHED/CMA data, maximize the utility of generic data, and standardize study design and methods. The FIFRA Scientific Advisory Panel (SAP) met in January 2007 and agreed with the need for new studies, the soundness of the "generic principle," and the general methods and study designs proposed. In response to EPA requirements for new exposure studies for re-registration of antimicrobials, members of the antimicrobials industry met in 2004 to share technical and financial resources to design and execute a new antimicrobial exposure monitoring program. The primary objective of AEATF-II is to develop handler exposure monitoring studies that will estimate and characterize exposure distributions for a number of occupational/industrial and consumer exposure scenarios that involve antimicrobial products.

The scope of the AEATF-II program was defined through consultations with EPA, Health Canada, and the California Department of Pesticide Regulation. The program focuses first on handler exposure, followed by monitoring of post-application exposures to residues on hard and soft surfaces. The program intends to cover the most common categories of antimicrobial pesticide use sites and the most common antimicrobial handler tasks.

A diverse and varied range of site categories have been identified, including agricultural premises and equipment, food handling premises and equipment, industrial process water systems, and drinking water systems. A number of commonly performed antimicrobial handler tasks also have been identified and characterized as segmented or complex tasks. Segmented tasks include activities such as mopping, wiping, pouring liquids, or spraying. Complex tasks include those associated with wood pressure treatments, using a brush or roller, and using an airless spray. Because studies of complex tasks will not be scripted, the Board will not review these protocols. In some instances, segmented tasks can be combined to form a distinct task. The AEATF mapped common tasks to use sites and defined a large number of scenarios that can involve use of different antimicrobial products. Because this represents too large a number to test individually, with the agreement of the Joint Regulatory Committee (JRC), the Task Force has decided that monitoring exposure incurred while mopping at one site would be applicable to the same activity performed at another site. In addition, some scenarios have been defined to include combinations of tasks; for example, the "mopping" task may also include disposing of

the used water. In some scenarios, such as testing aerosol spray use, only higher exposure variants are tested. In all situations, subjects will wear only the minimum required Personal Protective Equipment (PPE); workers who habitually wear more than minimal PPE will not be included in the study, because EPA believes that exposure calculated for such workers will not be easily extrapolated to workers who wear less.

Exposure monitoring is based on the assumption that exposure depends more on the characteristics of the use pattern than on the specific chemical tested. Exposure depends on the physical form and properties of the pesticides, application method, amount of pesticide used (which varies with duration), and user behaviors; therefore, the data obtained by monitoring exposure from use of one chemical can be used, with appropriate adjustments, to estimate likely exposure from similar uses of other chemicals. Monitoring of highly volatile materials will not be included in these studies because exposure might be differently affected by the physical properties of such materials.

AEATF-II has defined exposure scenarios as a set of similar uses of physically similar chemicals. Units in scenarios are handler-days and a "monitoring event" (ME) is a dataset fully describing a monitored handler-day (i.e., observations of one worker-handler). The target population is the universe of future handler-days; EPA wants to be able to characterize future exposures likely to result from use of a specific amount of an antimicrobial product in a well-defined exposure scenario. Each ME characterizes dermal and inhalation exposure for a single subject over at least half a day. The set of MEs for a scenario should characterize the range of expected exposures. The measured exposures from each set of MEs will be used to represent future handler-day exposures to antimicrobial pesticides used in a particular scenario.

AEATF-II plans to use an overall purposive sampling design to characterize a broad range of exposures in a small sample size. For this aerosol application scenario, testing will take place in guestrooms at three hotels/motels in the Fresno, California area, differing in the presence of kitchen facilities. The testing will be performed at different times, will use a wider range of quantity of pesticide handled (direct measurements of quantity will be performed), and will use different subjects (each subject will be monitored only once). Incorporation of random elements includes the sequence of screening hotels/motels to use as test sites, the sequence of contacting janitorial services providers, and the assignment of enrolled subjects to sites and ME slots.

EPA decided in November 2007, upon advice from the Board and others, to accept an overall purposive diversity sampling design for the AEATF-II monitoring program, with the requirements that AEATF-II must describe the sampling design for each scenario in detail; incorporate random elements whenever feasible; and document their rationale for using a particular approach, including all decisions regarding the feasibility of randomization of specific elements in the design. Diversity sampling, as defined by the Task Force, will maximize regulatory utility. This sampling strategy will maximize (within a small sample) diversity in conditions expected to influence exposure; ensure that different MEs differ with respect to factors likely to affect exposure; and increases the chance that the range of conditions expected to affect exposure in future handler-days is reflected in the set of MEs collected. The HSRB has noted in earlier reports that the resulting distribution of ME data is not statistically representative of exposures to the target population, and statistical inferences cannot be drawn from the results

of AEATF-II monitoring. The distribution has been deemed by EPA to adequately characterize for regulatory purposes the typical and high-end exposure values for a given scenario for the target populations of future handler-days.

AEATF-II study participants are expected to be experienced professional handlers of antimicrobial pesticides. They are recruited through flyers and newspaper advertisements; participants are not recruited through their employers. Qualified volunteers will be enrolled in the order of their response to recruiting efforts. The enrolled subjects are randomly assigned to monitoring sites and specific ME slots. AEATF-II study results will be reported to EPA in a monograph of each completed scenario. Scenario monographs will be reviewed by EPA and, for scenarios involving scripted exposures, by the Board. Upon acceptance, the data for each scenario will be entered into the Biocide Handlers Exposure Database (BHED™); data in this database are intended for use by regulatory agencies to model handler exposure. The aerosol application scenario is 1 of a number of scenarios that will provide data to be entered into BHED. Each scenario has 3 clusters, or sites, and each cluster has 6 MEs; 8 ME slots are defined for each site to allow for alternate participants.

Clarifying Questions

Dr. Johnson inquired whether 1 ME characterizes exposure for a single subject over half a day or an entire day. Mr. Timothy Leighton (OPP, EPA) explained that a "typical" work day would be defined in this scenario as the time needed to apply approximately 4 cans of product; the Task Force anticipates this will take between 30 and 180 minutes. Mr. Carley added that the studies are designed to ensure that exposure will be detectable for most of the MEs. The duration of exposure is designed to result in measurable residues. Dr. Philpott noted that the Board had previously recommended that EPA stratify by amount of active ingredient handled (AaiH) rather than time. Mr. Carley agreed, but explained that although the mopping scenario had accurate measures of AaiH, tiered active ingredient slots also were defined by duration; because people mopped at different rates, it was considered less intrusive and more accurate to tier AaiH by time. In the aerosol scenario, it will be possible to determine the AaiH. In response to a question from Dr. Chambers, Mr. Leighton explained that commercial products would be used in this scenario.

EPA Science Assessment: AEATF-II Aerosol Scenario and Protocol

Mr. Leighton provided EPA's science assessment of AEATF-II protocol AEA04. The aerosol application scenario will feature dermal and inhalation exposure monitoring during use of a hand-held pressurized aerosol-based end-use formulation containing an antimicrobial chemical. Participants will be provided with 19-ounce cans of the product and are expected to spray 4 cans. The scenario includes spraying a ready-to-use aerosol product until the treated surface is wet and excludes wiping the treated surfaces. The objectives of this protocol are to develop more accurate information on worker exposures to antimicrobials to support exposure assessment for aerosol spray applications. The data also will satisfy a requirement for new data imposed by EPA's Re-registration Eligibility Decision (RED) and will support Registration Review as well as pending and future registrations for various antimicrobial aerosol products and uses. PHED includes 2 spray scenarios, but the data are not considered to be entirely applicable

to antimicrobial aerosol spraying. The CMA study did not include sufficient MEs for the aerosol, used patch rather than whole body dosimetry, and reported low levels of residue.

The surrogate aerosol product was chosen based on its stable chemistry, appropriate vapor pressure (low), availability of robust and sensitive analytical methods to detect it, and exposure at the high end of the range for different aerosol product types (i.e., hard-surface disinfectant spray, soft-surface disinfectant spray, foaming aerosol spray, and air fresheners/sanitizers). Variables affecting exposure from aerosols include the amount of material used, release rate, particle size distribution (affects inhalation exposure), nozzle technology (affects particle size); can pressure, temperature and humidity at time of use; the surface on which the product is used; and the orientation of the can during use. Preliminary data estimates that approximately 1.3 grams (g) per second will be released by the aerosol product types. Surrogate selection included analysis of the variables affecting exposure, which showed that hard-surface aerosols are likely to provide the highest exposures and thus are appropriate surrogates for other aerosol types and uses. Details of the surrogate selection process are reported in Volume 1, Appendix A of the study.

The selected surrogate test material was Commercial Solutions® Clorox® Disinfecting Spray (EPA Reg. No. 67619-03). Active ingredients are 0.252 percent n-alkyl dimethyl benzyl ammonium chloride (ADBAC); 0.0945 percent didecyl dimethyl ammonium chloride (DDAC); 0.189 percent octyl decyl dimethyl ammonium chloride (ODAC); and 0.0945 percent dioctyl dimethyl ammonium chloride (DODAC). The dermal NOAEL reported in EPA RED for ADBAC is 20 mg per kilogram (kg) per day (mg/kg/day) for dermal irritation; no dermal toxicity data were available for low concentrations and no systemic effects have been observed. ADBAC inhalation NOAEL has been reported as 3 mg/kg/day, based on an oral study. Thus, the predicted dermal and inhalation margins of exposure (MOEs) will not be of concern. EPA relies on toxicity data on DDAC for all active ingredients in the DDAC cluster, including ODAC and DODAC. The DDAC dermal NOAEL reported in EPA RED is 1,000 mg/kg/day and 0.13 percent active ingredient (highest dose tested). No systemic effects and irritation have been observed. The proposed concentration in the test product is low. The DDAC inhalation NOAEL reported in EPA RED is 10 mg/kg/day, based on an oral study; therefore, the predicted dermal and inhalation MOEs for DDAC are not expected to be of concern.

The study will take place in Fresno County, California; this location was selected because indoor aerosol spraying tasks are not expected to vary geographically and the analytical laboratory is located in Fresno. The hotel/motel facilities will have sufficient appropriate surface to be sprayed and are readily available with varying configurations (e.g., full kitchen, kitchenette, or no kitchen). Sites will be selected after screening a list of all hotels/motels found in the Fresno County Yellow Pages. The properties will be selected in random sequence based on criteria including having 20 or more units; management willing to cooperate with the research; room configuration that provides a diversity of surfaces; function ventilation and electric systems; and does not require cleaning or maintenance before use. The first qualifying property will be selected for each configuration (full kitchen, kitchenette, or no kitchen).

Participants will be professional janitors to ensure that exposures are long enough to obtain usable data with exposures above the limits of detection. The study will enroll 24 subjects

and 18 will be monitored; each site will have 6 subjects and 2 alternates. EPA finds this sample size acceptable based on previous calculations. The rationale for sample size is consistent with all available aerosol data and exceeds the requirements of EPA and Organization for Economic Cooperation and Development (OECD) guidelines. No existing data can substitute for any of the proposed new MEs.

MEs will be stratified by amount of test material handled. The concentration of test materials will be constant and exposure will vary based on the amount handled and subject-specific behaviors. The minimum amount sprayed is 1 can to ensure detectable residues. The maximum amount sprayed is consistent with the amount sprayed per room (113 g per room) and an upper bound of 20 rooms cleaned per day. One ME at each site will spray 1 of 6 pre-defined amounts: 1 to 1.5 cans; 1.5 to 2 cans; 2 to 2.5 cans; 2.5 to 3 cans; 3 to 3.5 cans; and 3.5 to 4 cans.

Eight enrolled subjects at each site are ordered randomly, with the last two assigned as alternates. The first subject in the order will be assigned to the ME with the highest number of cans. Each subsequent subject is assigned to the available ME with the highest remaining number of cans. Subjects will follow label directions when spraying (spray 6 to 10 inches above the surface until it is thoroughly wet). Each subject will spray as they normally would on the job. Subjects will not wipe the surfaces after spraying.

Field measurements include air temperature and relative humidity in the hotel room; hotel/motel design and materials, such as sinks and toilets; characteristics of ventilation systems and the size of the room; the amount of material applied; and observations including videos and photographs. Whole body dosimeters will be used to measure dermal residues. Inner dosimeters (long johns) will provide an estimate of dermal exposure and outer dosimeters (normal work clothing consistent with label PPE) will provide an estimate of protection provided by a single layer of clothing. Subjects will perform a hand wash before breaks and at the end of the task. Face/neck wipes will be used at the end of the task. Personal air samplers will include both Occupational Safety and Health Administration Versatile Sampler (OVS) tubes and RespiCon filters. The OVS tube will be run at 2 L per minute (L/min) and the RespiCon filter will be run at 3.1 L/min. The RespiCon filter will size the particles (below 2.5 microns, below 10 microns, and below 100 microns) which will provide EPA with additional data concerning deep lung effects. The collected samples (dosimeters, hand/face washes, and air samplers) will be shipped on dry ice to the analytical laboratory and frozen within 4 hours. The QA/Quality Control (QC) plan includes field recovery analysis, travel recovery analysis, storage stability studies, and break-through analysis.

This protocol has addressed the technical aspects of applicable exposure monitoring guidelines, EPA Series 875 Group A – Applicator Monitoring Test Guidelines, OECD Applicator Guidelines, and Good Laboratory Practices (40 CFR part 160). Previous comments by EPA and the JRC have been satisfactorily addressed. The Agency has identified no scientific deficiencies that require correction. EPA has concluded that the protocol is likely to yield scientifically reliable information that would produce important information to fill an identified regulatory need (e.g., aerosol exposure data) that cannot be addressed except by research with

human subjects. The proposed research has a clear scientific objective, and a study design that should produce data adequate to achieve the objective.

Clarifying Questions

Dr. Lebowitz requested clarification regarding comparison of the OVS versus the RespiCon filter; these devices work differently and thus the data gathered by them will be difficult to compare. Mr. Leighton explained that gathering this data was viewed as a research opportunity for EPA rather than to allow direct comparison. Dr. Popendorf agreed that the samplers would provide different results and asked which the Agency intended to use. He also asked why each site was located in different types of buildings and why MEs would be performed one week apart. Mr. Leighton answered that SAP and HSRB discussions indicated that clusters can differ by time; therefore, the Task Force planned to perform monitoring at different times rather than all at once. Dr. Popendorf inquired if time between samples had been specified for the same location. Mr. Carley responded that monitoring at different clusters is separated by time based on the desire to sample under a diversity of conditions and obtain results with normal variation. If all monitoring is performed on the same day, conditions such as temperature and humidity will be similar. Monitoring on different days means the observations are more independent.

Dr. Popendorf questioned if samples would be spiked at the limit of quantitation (LOQ). Mr. Leighton replied that the analytical laboratory is confident that fortified samples can be spiked at the LOQ and the spiking can be detected. Biomonitoring data also will be examined to determine the accuracy of passive dosimetry. Dr. Philpott asked if the NOAEL information for dermal and inhalation exposures was based on data from acute or chronic exposures and if the Task Force was concerned that the participants would have pre-existing exposure from working with the test compounds on a regular basis. Mr. Leighton explained that EPA used repeat exposure studies to determine contact NOAEL.

<u>EPA Ethics Assessment: AEATF-II Aerosol Scenario and Protocol</u>

Ms. Sherman provided EPA's ethics assessment of the AEATF-II protocol AEA04. This research is likely to be of value to society because reliable exposure data for aerosol antimicrobial products are needed to support EPA exposure assessments and existing data are inadequate. The knowledge likely to be gained from this work will be usable in exposure assessments for both professional users and consumers and for a wide variety of aerosol products and use patterns.

Participants will be recruited from professional janitorial workers in Fresno County. Workplace flyers in English and Spanish will be posted and advertisements will be placed in three Fresno newspapers, including a Spanish language paper. Calls from individuals responding to the flyers or advertisements will be received by a field researcher; the flyers identify one field researcher as bilingual in English and Spanish. Callers are informed about the study using an IRB-approved script. The callers are screened for janitorial experience and other eligibility factors and then scheduled for informed consent meetings "at the caller's convenience." The consent process is essentially the same for English- and Spanish-speakers; the bilingual

researcher will conduct the first part of the process, if necessary, and the principal investigator will join in at the end of the meeting. The interested candidates will be provided with information about study design in the candidate's preferred language, eligibility criteria will be provided, and applicants will review the informed consent document and the "Experimental Subject's Bill of Rights." The principal investigator will provide product labels and the Material Safety Data Sheet and answer any questions the applicant may have. The principal investigator will confirm understanding and solicit consent to participate.

Some changes to the consent process have been made. Unlike earlier AEATF-II mop and wipe studies, the list of candidates responding to flyers or advertisements will not be randomized before scheduling consent interviews. The Task Force learned from previous studies that delaying informed consent meetings to allow randomization of lists leads to significant attrition. Thus, EPA has agreed to this change and considers that this proposal nonetheless complies with its direction to incorporate random elements whenever feasible.

EPA found the recruiting and consent process to have equitable subject selection, fully informed choice, and fully voluntary choice. Appropriate inclusion and exclusion criteria have been defined. Excluded from participating are subjects with skin conditions on their hands; allergies to household chemical products; cardiovascular disease; or severe respiratory conditions. Pregnant or nursing women; those who do not read, speak, or understand English or Spanish; and employees or relatives of the principal investigators or sponsors also are excluded. Coercion to participate was minimized by conducting private interviews and by having the potential subjects initiate interest.

Respect for participants is sufficient. Participant privacy will be maintained and any photographs or videos will be altered to protect subjects' identities. The proposed remuneration is reasonable and participants will be free to withdraw at any time, for any reason. Risks also have been minimized. To minimize risk of an irritant response to the test materials or solvents used to obtain residues from hands and face/neck, subjects with skin sensitivity or irritation will be excluded. To minimize discomfort or risk of heat-related illness due to the extra layer of clothing and air pump, stopping rules have been established, investigators will carefully observe the participants, and medical assistance will be available. To minimize embarrassment while changing into the dosimeter, a private changing area will be provided and same-sex technicians will be available to assist. The investigators will not record the results of pregnancy tests and also will enroll alternate subjects to protect subject privacy in the event of an unexpected positive pregnancy test.

The research poses no direct benefits to the subjects. There is potential indirect benefit to subjects who learn their individual exposure results and how those compare to the results of others. The sponsors will benefit by maintaining regulatory compliance. The likely societal benefit is higher quality exposure and risk assessments for aerosol antimicrobial products. EPA judges the risks to have been effectively minimized, residual risks to the subjects will be low, and the risks are reasonable given potential societal benefits.

The Independent Investigational Review Board, Inc. (IIRB) of Plantation, Florida reviewed and unanimously approved the protocol and supporting documents in English and

Spanish. The IIRB-approved protocol was re-dated prior to submission to EPA, but AEATF-II has confirmed that the version submitted to EPA is identical to the version approved by IIRB, despite having been re-dated after IIRB approval. In future submissions, AEATF-II must maintain a version date as a permanent attribute of the file, to maintain the integrity of the record. Because this is a proposal for third-party research involving intentional exposure of human subjects to a pesticide, with the intention of submitting the resulting data to EPA under the pesticide laws, the primary ethical standards applicable to this research are 40 CFR part 26, subparts K and L.

Corrections requested by EPA include clarification of compensation for research-related injuries (change "We will pay for needed medical treatment that is not paid for by your own insurance or by someone else," to "...by your own insurance or by the insurance of a third party under which you are covered") and instituting version control in all study documents. The protocol is in compliance with all requirements of 40 CFR §26.1111, §26.1116, and §26.1117, and of §26.1125 and §26.1203. If the requested corrections are made, the AEATF-II Aerosol Scenario and Protocol will likely meet the applicable requirements of 40 CFR part 26, subparts K and L.

Clarifying Questions

Ms. Sherman clarified that participants are not required to have insurance. Dr. Northington Gamble inquired if other hotel guests would be informed about research taking place in the hotel. She noted that community flyers warned about the research taking place, but EPA's ethical assessment did not consider whether bystanders could be harmed.

Dr. Parkin questioned how the investigators would determine if a volunteer was a resident of Fresno County. Ms. Sherman explained that volunteers would be required to provide identification (ID). Dr. Parkin recommended that this information be included on the recruitment flyer. She also requested clarification of the meaning of "vulnerable population." Ms. Sherman clarified that in this context, it primarily refers to avoiding coercion to participate. Dr. Parkin asked when and how participants are informed that they can request their individual exposure results. Ms. Sherman responded that this information was provided on the informed consent form.

Clarifying Questions for the Principal Investigator/Sponsor

Dr. Bryce David Landenberger (The Dow Chemical Company, on behalf of the AEATF-II Task Force), Dr. Sami Selim (Study Principal Investigator, Golden Pacific Laboratories), and Dr. Jeffrey Driver (Consultant for the AEATF, Infoscientific.com) responded to questions from the Board.

Dr. Selim addressed Dr. Popendorf's question concerning field spikes. He explained that the samples would be analyzed by high-performance liquid chromatography-mass spectrometry using an internal standard to quantitate DDAC in the sample. This technique is highly sensitive and selective. Before working with the samples, technicians will determine background levels of DDAC and ADBAC; DDAC and ADBAC are commonly detected in part because the detection

techniques used are highly sensitive. The major factor determining the LOQ is background levels of ADBAC and DDAC. The samples will be spiked in the field at the LOQ and with a higher level to bracket the predicted study sample levels. All matrices will be fortified as well. The air sampling tubes are spiked and then air is run through them for the same amount of time that the participants will be working and breathing through the tubes. Dr. Popendorf expressed concern about using the LOQ as the lowest spike amount because if any sample is lost, measurements will not be possible. He suggested spiking the samples at two to three times the LOQ. Dr. Selim corrected that the field samples will be at approximately four times the LOQ and laboratory-fortified samples will be spiked at the LOQ. This will be performed for every matrix used.

Dr. Northington Gamble asked how guests at the hotels at which the study would be conducted would be informed about the research. Dr. Landenberger explained that the Task Force is considering renting an entire floor or wing, or perhaps the entire hotel if it is small. Dr. Northington Gamble questioned language in the community flyer that counseled people not to be alarmed if they saw workers in PPE and also provided a number to call with concerns. She clarified that she was not concerned that hotel guests would be hurt by the research, but rather how to address any concerns they may have.

Dr. Philpott asked how the Task Force would ensure that participants were residents of Fresno County and how possible harm to undocumented workers would be avoided. Dr. Landenberger answered that the investigators participating in the recruitment process would not ask about residency status. A government-issued ID would be required for participation, per regulations established by the state of California. Volunteers without an ID will not be permitted to participate in the study. During recruitment for the mop and wipe scenario, volunteers who were not able to produce an ID were not enrolled and the issue was not pursued any further. ID materials are used to ensure that the participant is a resident of Fresno County and older than 18 years of age. Dr. Northington Gamble suggested that the recruitment flyer be changed to inform volunteers that ID materials are required in order to participate.

Dr. Johnson inquired if the 6 subjects at a single hotel would be spraying the same areas, and if so, whether measures would be taken to ensure that surfaces were dry between sprayings. Dr. Selim replied that the protocol called for using 20 rooms to try to avoid this issue; this part of the protocol may need to be clarified.

Dr. Parkin questioned how the Task Force defines "vulnerable" populations. Dr. Landenberger responded that the governing documents and protocols describe issues related to vulnerability, such as pregnancy, nursing status, or likelihood that a participant could be coerced. The Task Force has taken a number of steps to eliminate the possibility of coercion, such as avoiding employers in the recruitment process. The Task Force has discussed these matters extensively with EPA.

Dr. Popendorf asked if the Task Force had considered including housekeepers as well as janitors, because housekeepers may be less experienced than janitors and more likely to have higher exposure levels. Mr. Leighton answered that the JRC had considered this matter, as well as including consumers in the study; however, the JRC ultimately decided that there was unlikely

to be significant differences in spraying among janitors, housekeepers, and consumers. He acknowledged that EPA had no data to support this conclusion. Dr. Driver referenced a previous survey that showed that consumers tend to use less product than occupational users; thus, using janitors will allow data to be gathered for higher ranges of use and will allow greater diversification of the amounts applied. Dr. Popendorf argued that the consumers might use different techniques that increase their exposure.

Dr. Landenberger clarified that each hotel room would be used by only 2 subjects per day. The Task Force anticipates that the same room would not be used twice, even at the higher tiers of aerosol spray use.

Public Comments

Dr. Philpott invited oral public comment on the proposed AEATF-II research on exposure of janitorial workers applying antimicrobial pesticides formulated as aerosol sprays. No oral public comments were presented.

Charge Questions

If the proposed AEATF-II aerosol application scenario and field study protocol AEA04 is revised as suggested in EPA's review and if the research is performed as described:

- Is the research likely to generate scientifically reliable data, useful for assessing the exposure of handlers who apply antimicrobial pesticides formulated as aerosol sprays?
- Is the research likely to meet the applicable requirements of 40 CFR part 26, subparts K and L?

Dr. Philpott reminded Board members that they had previously reviewed two Task Force scenarios (wipe and mop protocols) and approved them while indicating some concerns about field conditions, similar to what was discussed for the aerosol spraying scenario. The Task Force appears to have addressed many of these concerns. He also reminded the Board that they had agreed that purposive diversity sampling would be acceptable as long as a well-developed sampling frame was used, sampling incorporated random elements where possible, and an adequate AaiH range was used.

Board Science Review: AEATF-II Aerosol Scenario and Protocol

Dr. Lebowitz opened the Board's science review by stating that the process used to select the test product was rational, the design has incorporated random elements, the scenario was well defined, and exposure also was well defined and was anticipated to describe that of typical occupational exposure. Exposure monitoring and QA/QC procedures are adequate and sufficient variation in exposure is likely to occur. Weaknesses to the study include lack of inclusion of consumers; previous studies have shown differences in exposures between lay and professional users of aerosol sprays. The assumption that exposure is proportional to AaiH may be incorrect. No statistical analyses were included; results will be reported in a descriptive manner. The

protocol also does not call for collection of data for exposure arising from wiping the sprayed surfaces. The exclusion criteria should include immuno-compromised people because exposure to antimicrobial products might pose a health risk to them. He concluded that the proposed study was scientifically valid and likely to yield reliable results.

Dr. Popendorf stated that he approved of the protocol. He suggested that the Task Force consider performing partial sampling of a consumer population, independent of this protocol. The scheduled use of the hotel rooms for the study should be clarified to ensure that subjects are not spraying wet surfaces, which could affect exposure. Use of two different types of air sampling devices likely will yield different results and the Task Force and EPA must consider how it will use these results. He agreed that creating two separate protocols for spraying and wiping was logical, but asked whether the subjects might automatically attempt to wipe the surface after spraying, which would likely affect exposure. Dr. Chambers asked if Dr. Popendorf was recommending rejecting any data gathered from subjects who inadvertently wiped the sprayed surface or excluding "sloppier" workers. Dr. Popendorf clarified that he was asking how EPA and the Task Force would use a data point that indicated exposure significantly above most of the other data points gathered in the experiment. Dr. Young stated that "sloppier" workers should be included to capture natural variation in techniques. Mr. Leighton acknowledged Dr. Popendorf's concerns, but explained that workers would not be provided with a rag, and thus would be unlikely to wipe the surface. He added that because the point of the experiment was to capture a range of exposures, data from workers who accidentally placed their hands on a sprayed surface during spraying needed to be included.

Dr. Johnson remarked that his primary concern about the protocol was the use of 6 tiers of spraying. He asked how the Task Force would ensure that subjects sprayed only half a can or sprayed the entire can. Dr. Parkin noted that the categories overlap. Mr. Carley replied that the cans could be half emptied before being given to the workers. The cans also will be weighed, so it will be possible to determine how much product a worker sprayed in a given time period to confirm inclusion of their data in a given monitoring tier. Dr. Johnson recommended that the protocol specifically address this issue.

Dr. Philpott summarized that the Board believes the protocol is likely to yield scientifically reliable data for assessing exposure from aerosol spraying. There was some concern that limitation of use to professional janitors might not capture all information about potential users. A bridging study to explore differences in use between professional janitors and consumers was suggested. The Board suggested that EPA and the Task Force carefully consider constants in their exposure calculations that might actually be variable. The Board did not recommend excluding "sloppy" workers because their data will be needed to capture the full range of exposure; however, the Board did have concerns about how extreme outlier data would be used. Mr. Carley clarified that the protocol called for excluding data from workers who grossly violated the protocol; this would include workers who inadvertently wiped a surface after spraying it.

Board Ethics Review: AEATF-II Aerosol Scenario and Protocol

Dr. Menikoff praised EPA's ethics review for this protocol and agreed with the Agency's analysis. The justification of the use of ADBAC was sound. He disagreed with the conclusion that no vulnerable subjects would be included, but agreed that the study was exceptionally well designed to protect them. The language used in the informed consent form seemed to be of an inappropriately high level, given the expected educational levels and language skills of the participants. Dr. Menikoff concluded that the study was very well designed and that exceptional efforts had been made to minimize risks to subjects.

Dr. Northington Gamble agreed with Dr. Menikoff's conclusions. She complimented the use of community flyers to inform hotel residents about possible risks, but noted that these could be improved. She suggested that the recruitment flyers be changed to inform potential subjects that government ID was needed for participation. She concluded that the protocol met the applicable ethics standards.

Dr. Lebowitz asked that the medically vulnerable (e.g., immuno-compromised people, people with severe type II diabetes, or chemotherapy patients) be excluded from the study.

Dr. Philpott summarized that the protocol will meet the applicable ethics requirements. Recommendations were made to improve the community flyers explaining risks to hotel guests if the Task Force does not rent the entire hotel. Recruitment materials should mention the requirement for government ID materials, the Spanish translation of the materials should be checked, and appropriate use of lay language confirmed. He stated that the Board would not need to review this protocol again before execution.

Chair Summary of Recommendations

Dr. Philpott provided a summary of Board deliberations and conclusions from Tuesday, October 20, 2009. He reminded EPA that Board recommendations were not binding until the Board report had been finalized and approved.

Newton and Breslin Study (1983)

The Board recognized substantial limitations to the Newton and Breslin study and recommended that EPA use caution when including the data in its white paper. Use of the data should be limited to careful consideration of its qualitative contribution to the overall WOE only. Regarding the relevance of the data to assessment of the relationship between pyrethrins/pyrethroids and asthma, the study provides some data to assess the association of this particular aerosol with respiratory effects, but the lack of appropriate controls means that the effects cannot be conclusively determined to have arisen from exposure to pyrethrins/pyrethroids. Dr. Lebowitz suggested that rather than state that controls were lacking, the Board should explain that appropriate follow-up exposure to the components of the product were needed to determine if pyrethrins/pyrethroids were responsible for the effects observed. In addition, the testing performed did not follow standard protocols for examining responses to the product; for example, an improper bronchodilator challenge was used and the early histamine

challenge was improperly performed. Dr. Lehman-McKeeman clarified that as lead writer, she found that a relationship between pyrethrin/pyrethroid exposure and allergies or asthma could not be concluded from this study. At best, the data are applicable only to the tested product. Dr. Philpott agreed that this could be explained further in the Board report. Mr. Jordan confirmed that the Agency understood and agreed with the Board's advice concerning these data.

Dr. Philpott listed some limitations of the study, and acknowledged that additional issues might be described in the Board report. Limitations included the small sample size, incomplete description of methodologies used, lack of complete data for most patients, lack of appropriate controls, lack of statistical analyses, and use of subjective responses. Regarding the ethics of the study, the Board found no clear and convincing evidence that the study was fundamentally unethical or significantly deficient in its conduct.

Lisi Study (1992)

Dr. Philpott reviewed the Board's recommendations for the Lisi study. The study report was brief; therefore, it was difficult to evaluate the methods used and the data. EPA should use these data with caution and limit its use to careful consideration of its qualitative contribution to the overall WOE, particularly within the framework of hazard identification. Dr. Lehman-McKeeman suggested that EPA's charge question asks for a yes or no answer, but the Board did not provide either response. The Board offered a highly qualified answer because of the study's limitations. She added that the Board concluded that the data are, at best, applicable to the specific product that was tested, period.

Regarding whether the data provide evidence of a relationship between pyrethrins/pyrethroids and dermal irritation, the Board found that the report provides some data to assess the association of the compounds tested, particularly the cyanopyrethrins, with an effect. The low response rate and information contained in footnote #1 to the data table suggests that the reactions are likely to be irritant responses. Dr. Popendorf noted that two of the responses are likely to be allergy or sensitivity responses. Dr. Philpott agreed to discuss this issue in greater detail in the Board report. Dr. Chambers cautioned against implying that all cyanopyrethrins may have a dermal effect, given that only two of the four tested in this study had an effect. Dr. Philpott agreed that the two responses do not necessarily implicate an entire class of compounds, but stated that this matter should be included in the Board report. He described limitations to this study, including the limited description of the methods used, uncertainty about subject compliance, lack of controls, and poor statistical analyses. The Board found that the study was not conducted in an unethical manner, given the extremely limited information available.

AEATF-II Aerosol Application

The Board concluded that this protocol was likely to yield scientifically reliable and useful data, if revised as recommended and performed as described. Recommendations for improvement included considering consumer users (in this or subsequent studies), developing criteria for excluding data from participants who deviate grossly from the protocol, considering likely differences in the air sampling results arising from the use of two different samplers, and

considering other variables that may influence exposure. Overall, the Board believed that the protocol, if revised as recommended, was acceptable and does not need to review it again before execution.

Dr. Popendorf suggested two changes, including that the suggestion for a consumer use study not be given as a recommendation because it is beyond the purview of this particular study. He added that field spikes should be made at levels above the LOQ. Mr. Jordan clarified that the protocols use of the phrase "exclusion of participants who deviate grossly from the protocol" implied involuntary withdrawal. Dr. Popendorf noted that this issue is explained in the informed consent form and suggested that it be elaborated upon in the protocol.

Dr. Philpott summarized that the Board found the protocol to comply with relevant ethical standards. The Task Force should consider broader community notification and reconsider the reading level and idioms used in the English and Spanish versions of the informed consent forms. The exclusion criteria should be expanded to exclude immuno-compromised people or those who may be at increased physical risk if they participate in the study. The recruiting materials should be revised to include the requirement for government ID.

Review of June 24-25, 2009 HSRB Meeting Report

Dr. Lewis stated that upon review and final approval of the June 2009 HSRB meeting report, the finalized report will be posted at www.regulations.gov. Review and finalization of the report is a public process; public comments have been solicited, but none were received. After the review, Dr. Lewis will work with Dr. Philpott to incorporate comments and revise the report, after which the final document will be released.

Dr. Philpott began the review of the Board report with the Nolan et al. pre-Rule chlorpyrifos study, in which participants received a single oral or dermal dose of chlorpyrifos. The Board concluded that the data were at the limit of detection and therefore not useful. Measurements of TCP in urine were likely to be reliable, but blood measurements were not because of questions concerning methods used to detect TCP conjugates in the blood. New data regarding these matters have been received from Dow and will be considered by EPA in its re-evaluation of this study's utility. The Board also expressed concern about the variability of the erythrocyte cholinesterase activity but decided that these data were likely to be reliable. The Board concluded that the data were reliable, with reservations about the data describing effects on erythrocyte cholinesterase activity, given that only a single dose was used for this part of the study. The Board also found no clear and convincing evidence that this study was conducted in an unethical manner.

The second chlorpyrifos study, by Honeycutt and DeGeare, was a worker re-entry exposure study. The Board found the blood and urine measurements of chlorpyrifos and/or TCP likely to be reliable but of limited value, given the small sample size, failure to account for background chlorpyrifos levels, incomplete urine collection data, and high degree of variability in the daily measurements. Measurements of cholinesterase activity and inhibition were accurate and reliable, but of limited utility because of the lack of controls, small sample size, collection of only one measurement, and dose estimation based on dermal exposure data. The Board found no

clear and convincing evidence that the study was unethical or conducted in a significantly deficient manner relative to the prevailing standards.

The third chlorpyrifos study, by Kisicki, was a rising dose toxicity study to determine a NOAEL for erythrocyte cholinesterase inhibition and blood and urine TCP levels at three dose levels. The Board had concerns about the analytical methods used, lack of control for detecting glucuronidase conjugated TCP, and discrepancies in absorption measurements between this and the Nolan study. The Board questioned the utility of these data for risk assessment activities. Measurements of cholinesterase activity and inhibition are likely to be reliable, but the Board raised concerns about relying on incomplete data from the subject exposed to the highest dose. The statistical analyses were not appropriate and EPA should perform these analyses correctly if it chooses to use the data for model development.

Regarding the ethics of the Kisicki study, the Board had concerns about its conduct, particularly in the area of informed consent. It was unclear if appropriate consent to participate had been obtained from the subjects; however, given information provided during and after the meeting, the Board could not conclude that there was clear and convincing evidence that the study was unethical or significantly deficient. Therefore, EPA is not prohibited from using the data from this study.

The Board also reviewed a completed study from ICR, Inc., which was a laboratory-based study of the efficacy of 20-percent picaridin cream and spray formulations in repelling stable flies. The Board had concerns about whether this work would provide valid results for assessing efficacy against stable flies. The Board recommended corrections to the statistical analyses described in the report, namely that the standard error and confidence interval calculations for the mean protection time should use estimated protection time. The Board concurred with EPA that the study was in compliance with the pertinent ethical standards.

Dr. Philpott suggested that a statement on page 26, line 11 to 12 of the report be changed to reflect that this study uses first bite, rather than confirmed bite, to judge efficacy failure. Mr. Carley suggested using the term "unconfirmed bite." Dr. Lebowitz countered that use of the word "unconfirmed" implies that a second bite is not needed to confirm the first, which might be incorrect. Dr. Philpott clarified that the issue was whether landings with intent to bite could be used instead of bites and whether use of bites is justified. The correction would clarify that use of bites is acceptable, rather than confirmed or unconfirmed. Mr. Carley clarified that EPA understands the use of "unconfirmed" bites to mean that a bite is evidence of product failure and a second bite is not needed to confirm failure. For regulatory purposes, the use of first bite as an endpoint, unconfirmed by a second bite, is acceptable. Dr. Philpott agreed to change the phrase to read that use of the first bite as an endpoint, unconfirmed by a second bite, is acceptable.

The Board discussed its review of the Carroll-Loye Biological Research, Inc. (CLBR) Protocol LNX-002. This study tested the efficacy of 20-percent picaridin cream and spray formulations against biting flies in the field. The Board agreed with EPA that if modified and conducted as indicated, the study would yield scientifically valid and reliable data. Recommendations made by the Board included considering whether the standard for confirming bites might result in right-censored data. The Board also requested additional explanation and

justification of exposing the subjects to biting flies for 2 minutes every 30 minutes, rather than 1 minute every 15 minutes as had been done in previous protocols. Differences in biting behaviors and aggressiveness of different biting fly species should be considered. Accurate calculations of mean protection time should be made. The Board concluded that if the protocol is modified according to EPA and Board recommendations and is executed as modified, the protocol will be conducted in compliance with ethical standards.

The Board reviewed an Agricultural Handlers Exposure Task Force (AHETF) protocol, AEH120, which will test exposure during mixing and loading of pesticides in water-soluble packages. Given the lack of existing reliable and scientifically sound data on agricultural handler exposure to pesticides, the Board agreed that the proposed protocol would generate scientifically valid data that might be useable for assessing exposure during mixing and loading processes. However, the data might not be useful for creating distributions of worker exposure that are scientifically accurate and precise. The Board had concerns about the use of the words "accurate" and "precise" because sound science requires precision. Dr. Philpott suggested that "scientifically accurate" be substituted for these words. Dr. Lebowitz noted that these words are used differently in different disciplines. An acceptable scientific study that uses crude measurements might not yield a certain level of precision (for example, as determined by the number of decimal points used in reporting a measurement), but may nonetheless be accurate, if "accuracy" is defined as deviation of the measurements from true values. He asked whether the Board was questioning the accuracy or the precision of the proposed measurements. Dr. Philpott explained that the rest of the recommendation advised that EPA should use caution in determining if the data are useful for creating a distribution of worker exposure. Dr. Lehman-McKeeman suggested combining the two sentences, such that the Board advises that the data be used with caution for determining a distribution of worker exposure and can be used in such a manner only if exposure is proportional to AaiH. Dr. Popendorf said that testing 25 subjects alleviates concerns about precision; accuracy might be affected because of the study design. Dr. Young noted that all studies are based on the assumption that exposure is proportional to AaiH; however, in her opinion, EPA has not carefully considered how to handle the data if this assumption does not hold. Dr. Chambers suggested that Dr. Lehman-McKeeman's solution be adopted because the Board did not criticize the analytical methods proposed; accuracy and precision have distinct definitions in the field of analytical chemistry. The Board agreed to this change. Dr. Philpott summarized that the sentence would be changed to reflect the Board's advice that the data are useful for creating a distribution of worker exposure only if exposure is proportional to AaiH. Dr. Philpott added that he also recommend that the AHETF and EPA acknowledge the limitations of the data and add appropriate statistical and data management tools such that these limitations are not forgotten once the data have been entered into PHED to avoid use of the data to generate statistical distributions in the absence of knowledge about the limitations.

Dr. Philpott summarized that if modified according to Board and EPA recommendations, the protocol will meet the applicable ethical requirements. The Task Force should implement the changes suggested regarding informed consent forms and recruitment. Regarding release of individual exposure data, the Board recommended that the Task Force release the data only once the study is complete, except in cases where the data indicates an unusually high level of exposure and if the data can be used to mitigate exposure risks. There was some concern about

releasing the data as it is collected, and also that workers finding that their exposure was low might be less cautious about avoiding exposure in the future.

Dr. Philpott stated that he and Dr. Lewis will make these and other minor grammatical changes to the report. The Board unanimously approved the report for the June 2009 HSRB meeting.

Proposed CLBR Study (LNX-003): Efficacy of Two Picaridin-Based Personal Insect Repellent Formulations Against Ticks

Background

Ms. Sherman provided an overview of the proposed study LNX-003. This is the third in a series of tests of this picaridin formulation against biting insects proposed by CLBR. LNX-003 tests the efficacy of two formulations containing 20-percent picaridin against ticks in a laboratory setting. Protocols LNX-001 and LNX-002 were reviewed favorably by the Board at previous meetings; these protocols were field studies to test the repellent efficacy of the same two formulations against mosquitoes and biting flies.

Based on advice from the Board, CLBR amended LNX-002 to include dosimetry testing on 15 additional subjects for the cream formulation. This work found a 40 percent lower mean dosing rate in these subjects compared to previous dosimetry testing; the data also were less variable. The resulting pooled application rate was closer to historical industry standards for cream formulations of repellents. LNX-003 proposed to use the typical consumer dose established in LNX-001, augmented by the additional dosimetry data for the cream formulation from LNX-002.

The test materials described in LNX-003 are the same as those used in field studies to test repellency against mosquitoes (LNX-001) and biting flies (LNX-002). The protocol is similar to the tick repellent laboratory studies from CLBR previously reviewed by the Board in October 2006 and October 2007. The new protocol format incorporates previous EPA and HSRB comments, which has streamlined the organization of the protocol; however, the reorganization of this tick study protocol was less successful than the previous protocol reorganization, and further editorial corrections and clarifications are needed; these are easily correctable.

This submission meets the standards of completeness defined in 40 CFR §26.1125 and is ready for Board review. The initial submission was supplemented by a September 16, 2009 memorandum from CLBR to EPA describing planned protocol revisions in response to EPA concerns regarding editorial errors and ambiguities in the protocol. EPA believes that CLBR will adequately revise the protocol to correct the noted editorial errors.

EPA Science Assessment: LNX-003

Mr. Kevin Sweeney (OPP, EPA) presented the Agency's science review of LNX-003. The objectives of this protocol are to determine complete protection time (CPT) in the laboratory

against two species of nymphal ticks by two repellent formulations containing picaridin and to satisfy a condition of registration imposed by EPA. The products to be tested are EPA Reg. Nos. 39967-50 (lotion) and 39967-53 (pump spray). Both formulations contain 20-percent picaridin. The oral lethal dose 50 (LD50) is greater than 5,000 mg/kg and the dermal LD50 is greater than 2,000 mg/kg. Based on standard dose rates and average skin area covered, the lotion formulation is expected to have an MOE of 465 for arms and the spray formulation is expected to have an MOE of 541 for arms; both these values are well above EPA's target MOE of 100.

This study will involve up to 23 subjects who will be trained in the laboratory to handle laboratory-reared, pathogen-free ticks and to remove them before they can bite. The product will be applied to one arm of the subject and the other arm will be untreated. Treatments will be randomized to the right or left arm within each gender. Ten subjects will be assigned to each treatment; this sample size has been deemed adequate in previous tick studies and exceeds EPA guidelines for repellent testing.

The ticks used in the study are *Ixodes scapularis*, the main vector of Lyme disease, and *Dermacentor variabilis*, the main vector of Rocky Mountain Spotted Fever. Each tick will be used only once. Ticks will be qualified by being placed on the untreated arm of each subject to ensure that only actively questing ticks are used in efficacy testing. The endpoint is the First Confirmed Crossing (FCC) for each species. Each tick is evaluated for active questing by placing it on the wrist of the subject's untreated arm and must move at least 3 centimeters (cm) toward the elbow within 3 minutes to qualify. The qualified tick is then placed on the wrist of the treated arm; if the tick crosses at least 3 cm into the treated area within 3 minutes, it is scored as a crossing.

Both tick species will be tested within each 15-minute cycle. During each cycle, a tick of species #1 is qualified, which may take 3 minutes or more. The qualified tick of this species is then tested on the treated arm for 3 minutes. A tick of species #2 is then qualified, and if qualified, placed on the treated arm for testing. This cycle is repeated every 15 minutes until efficacy failure or for 12 hours. Efficacy failure for each tick species is defined by the FCC. The FCC is a crossing into the treated area confirmed by another crossing by a tick of the same species within either of the two subsequent test periods (e.g., within 30 minutes of the first crossing). Data from each tested product on each tested species will be analyzed and the mean CPT (mean time from treatment to FCC), median CPT, and Kaplan-Meier median value will be reported.

The proposed amendment language sent by CLBR on September 16, 2009 addresses most of EPA's concerns. The experimental procedure needs to be clarified and harmonized with the description found in the informed consent form. Additionally, EPA has requested clarification to address response if all required events cannot be conducted within a given 15-minute testing period. If these concerns are addressed, the Agency believes that the protocol should yield data that are scientifically sound and that may be used to assess the repellency of the tested formulations against ticks in the laboratory.

Clarifying Questions

Dr. Chambers asked if the FCC required crossing in 2 subsequent test periods. Mr. Sweeney answered that this was how crossings would be considered confirmed. Dr. Young requested clarification regarding where the tick is placed relative to the treated area. Mr. Sweeney explained that lines are drawn every 3 cm on the arm from wrist toward the elbow and the tick will crawl toward the elbow as ticks tend to crawl upward. The placement of the tick below the treated area is clearly defined in the protocol.

Dr. Green commented that the testing cycles appeared to be highly complex, given that both qualifying and testing of both species of ticks must occur in each cycle. Mr. Sweeney agreed, and noted that the Agency had questions concerning how data would be recorded if these required activities could not be completed within a single cycle. Dr. Johnson inquired why the protocol mentioned using a paintbrush to move the ticks. Mr. Sweeney responded that the paintbrush was used to gently orient the ticks and prompt them to move toward the elbow.

EPA Ethics Assessment: LNX-003

Ms. Sherman provided EPA's ethics review of LNX-003. Given the serious public health risks posed by tick bites, the proposed study provides value to society by providing an alternative to other available tick repellents. Both test formulations are conditionally registered; product-specific efficacy testing is required to support label claims of repellency against ticks.

Participants will be recruited from among previous CLBR testing subjects who have expressed interest, supplemented by word-of-mouth notification about the protocol. Inclusion and exclusion factors are well defined and appropriate and no eligible subjects are from populations who would be especially vulnerable. EPA has asked CLBR to remove the final two exclusion criteria, which are not properly applied prospectively and are more appropriate for managing subject withdrawal. EPA has found CLBR's proposed consent procedure to be appropriate.

Risks to participants include possible eye irritation if the products contact the eyes, and harm if swallowed. To mitigate these risks, the products will be applied directly to the arms using a syringe. Risk of exposure to biting arthropods is minimized by excluding participants with sensitivity to bites and training them to handle and remove the ticks before they bite. Exposure to arthropod-borne disease is minimized by using laboratory-reared, disease-free ticks. EPA has some questions regarding stress of participation, given the number of activities that must be completed within each 15-minute testing cycle. Another possible risk to participants is breach of privacy, primarily from pregnancy testing to exclude pregnant participants; appropriate procedures to protect privacy are described in the protocol.

This protocol provides no direct benefits to the subjects; the primary direct beneficiary is the sponsor. If the materials are proven effective and remain on the market, indirect beneficiaries will include repellent users who prefer one of these products to other repellents. CLBR has not overlooked any reasonable opportunities to further reduce risk while maintaining scientific robustness. The probability of residual risks to subjects can be accurately characterized

as "extremely small." Therefore, the risks to subjects are reasonable given the expected societal benefits of the knowledge likely to be gained.

IIRB reviewed and approved the protocol and informed consent materials. IIRB's complete policies and procedures, entitled "Human Research Protection Program Plan" (dated May 17, 2009) were included in supplemental submission of IRB materials. Descriptions of subject recruiting and consent processes are complete and satisfactory. The consent forms include all elements required by regulations and the language and reading level of the forms is appropriate.

Methods proposed for managing information about prospective and enrolled subjects will effectively protect their privacy. Subjects are free to withdraw at any time. The proposed level of compensation is appropriate ($20 per hour). Subjects who withdraw will be compensated for the time spent in the laboratory up to the point of withdrawal ($20 per hour plus an additional $50). Alternate subjects who are not needed will be compensated for their inconvenience. Medical care for research-related injuries will be provided at no cost to subjects.

This is a proposal for third-party research involving intentional exposure of human subjects to a pesticide, with the intention of submitting the resulting data to EPA under the pesticide laws. The primary ethical standards applicable to the conduct of this research are 40 CFR part 26, subparts K and L. Attachment 1 to the EPA Review contains a point-by-point evaluation of how this protocol addresses the requirements of 40 CFR part 26, subparts K and L and additional criteria recommended by the HSRB. EPA has found no specific deficiencies relative to 40 CFR part 26, subparts K and L, or to FIFRA §12(a)(2)(P) in its review of the protocol. The Agency has some concern about stress on subjects due to the demands of the testing regimen. The demands of the protocol appear to leave little opportunity for subjects to rest, eat, or use the facilities during the 12-hour testing period. EPA has also requested clarification about the definition of "research-related injuries."

The Agency has determined that this protocol satisfies all requirements of CFR 40 §26.1111, §26.1116, §26.1117, §26.1125, and §26.1203. If further revised to clarify ambiguities and correct the identified drafting errors, CLBR protocol LNX-003 will meet the applicable requirements of 40 CFR part 26, subparts K and L.

Clarifying Questions

Dr. Green raised questions about the lack of details from IIRB, regarding criteria for IRB review as detailed in CFR 40 §26.1111. During the science review, the Agency assessed whether IIRB was accredited and if so, by whom; the answer to this was not reported and this IRB is not listed as accredited. He inquired if this IRB had Federal Wide Assurance (FWA) from the Office of Human Research Protection (OHRP); this is listed as "not reported" or "not available" in the supporting documents. Ms. Sherman explained that accreditation and FWA are not required by EPA; IIRB meets EPA requirements. Dr. Philpott added that there are over 2,700 IRBs in the United States and few are accredited. Dr. Menikoff clarified that FWA is a commitment that research conducted by an IRB is in compliance with federal requirements, but because this IRB does not conduct research, it can be regulated by OHRP rather than through

FWA. He added that IRBs that accept federal funds are required to be registered with OHRP, but this is not an indication of meeting certain standards.

Clarifying Questions for Principal Investigator/Sponsor

Dr. Scott Carroll and Mr. Shawn King (CLBR) responded to questions from the Board. Dr. Philpott opened the questions by noting the Board's and EPA's concerns about the activities that must occur in each 15-minute testing interval, including how data would be managed if these activities cannot be completed in the allotted time and whether this places too much stress on participants. Dr. Carroll explained that because ticks are active and move quickly, completing the testing activities is not likely to be problematic. On average, it takes approximately 5 minutes to qualify a tick and once it is placed on the treated arm, it is quickly and clearly repelled by the treatment. He commented that CLBR proposed adding language stating that if the third tick of the second species is tested at minute 16, 17, or 18, the data would be assigned to the prior test interval. He also proposed language that would state that tick failure to quest is exceedingly rare. He acknowledged that the schedule was a busy one for subjects, but in his experience, it was not highly stressful and there would be adequate time for eating, resting, and using the facilities.

Dr. Popendorf inquired if Dr. Carroll had any information comparing behavior of laboratory-raised ticks to that of wild ticks. Dr. Carroll responded that he was not aware of any studies that compared behaviors directly. Most investigators prefer to work with laboratory-raised ticks to minimize the risk of disease. The ticks are usually raised for 5 or 10 generations in the laboratory. In the literature, within a given class of repellents the results of laboratory testing of laboratory-raised versus wild ticks are consistent; however, this has not been addressed rigorously. He added that he expected that the difference in behavior between laboratory-raised and wild ticks would be slight.

Dr. Popendorf questioned if Dr. Carroll had considered individual differences in susceptibility to tick bites. Dr. Carroll replied that there was little information in the literature regarding susceptibility to tick bites; some information was available to show that people vary in attractiveness for mosquitoes. Because gender differences have been shown for mosquito attractiveness, both men and women will be included in this tick study.

Dr. Green asked if attempts would be made to guide the ticks to ensure that they move from wrist to elbow. Dr. Carroll explained that ticks are placed distally to 3 lines drawn on the subject's arm. The center line indicates the edge of the treated area (the entire arm, except for the hand, is treated). The third line is located within the treated area. The tick must cross the third line for efficacy failure to be recorded. The distal line is used to ensure that the ticks are not placed directly on the treated area. Dr. Green inquired if the second tick would be affected by any excretions that might have been left behind by the first tick. Dr. Carroll explained that there was no basis for considering that this might be an issue. Ticks sensing the presence of other ticks might be attracted to the area rather than repelled, but there are no data on this matter. Dr. Carroll also clarified that the previously mentioned paintbrush would be used to gently align the ticks to move in the desired direction, not to forcefully move the ticks.

Public Comments

Dr. Carroll, CLBR

Dr. Carroll noted the Board's ongoing concerns about statistical evaluations of these protocols. The fundamental limitations have been the sample size. The historical norm for regulatory data has been 6 subjects, and recent protocols have increased this number to 10. Another issue is how to manage truncation of the data in long-lasting tests of repellents, because newer repellents are efficacious for long periods. He acknowledged having been initially unprepared for this outcome, but his laboratory has sought to address this issue by informing subjects about potentially long testing days and re-designing protocols to allow testing to last for longer periods.

Dr. Carroll acknowledged that it has been difficult for him to determine the best sample size for these studies. Larger sample sizes likely would be better, but there exists a robust body of literature on repellents tested on only 5 or 6 subjects and the resulting data were used for labeling purposes. He commented that to his knowledge, EPA had not received numerous complaints that repellents were not lasting for as long as indicated on the labels. He agreed that using 10 subjects resulted in better data, but use of more subjects must be balanced with sponsors' financial concerns. He also agreed that increasing the duration of testing has resulted in stronger data.

Charge Questions

If the proposed field repellency study protocol LNX-003 is revised as suggested in EPA's review and if the research is performed as described:

- Is the research likely to generate scientifically reliable data, useful for assessing the efficacy of the tested materials in repelling ticks?
- Is the research likely to meet the applicable requirements of 40 CFR part 26, subparts K and L?

Board Science Review: LNX-003

Dr. Chambers opened the Board's science review of protocol LNX-003 by stating that the protocol was likely to yield scientifically valid data. The Board's questions about various confusing issues, namely activities taking place within the 15-minute test cycles, had been answered. Inconsistencies in the protocol were addressed by the protocol amendment and probably resulted from carryover from other protocols; she advised more careful proofreading in the future. She noted that previous recommendations given by the Board for these protocols had been effectively incorporated into this most recent protocol. She commented that the protocol was easy to read, but long, and could perhaps include less justification of some activities. Dr. Chambers concluded that the protocol was likely to yield scientifically reliable and useful data for addressing product efficacy in repelling ticks.

Dr. Green agreed with Dr. Chambers' assessment. He noted that his concerns about the 15-minute testing intervals had been adequately clarified. He concluded that if changes recommended by the Board were made, the protocol would generate scientifically useful data. Dr. Young agreed that given the existing guidelines, the data are likely to be reliable; however, the Board has insufficient data to rigorously judge. She added that the word "blocking" is used inappropriately and the word "stratify" in reference to how men and women would be assigned for testing should be used instead. The sample size has not yet been adequately justified and might be too large rather than too small. Regarding the data censoring issue, EPA should consider whether the mean CPT is the best measure to use to judge efficacy. If the data have a symmetric distribution, mean CPT means that the product failed for half the subjects. Determining the percent of people covered for a given amount of time might be more constructive. Dr. Young concluded that the data probably would be reliable, based on existing repellent testing guidelines, but might not be if these guidelines are changed.

Dr. Popendorf asked if CPT is an average or measured for each person. Dr. Young answered that CPTs for individuals are based on the time to FCC. The mean CPT will be reported for all subjects, although this is usually highly censored data because there are few failures. If 3 or 4 failures occur, analyses that address censoring can be performed, but these usually are not done. If large amounts of the data are censored, the confidence intervals will be large.

Dr. Philpott summarized that, given the existing regulatory framework and guidelines, the Board has concluded that the protocol is likely to generate data that will be scientifically valid and useful for the Agency. The Board had some concerns about statistical validity and sample size. The Board suggested the investigators re-examine the use of statistical terms to ensure they are used appropriately, provide a clear justification for the sample size, address possible data censoring, and consider using the percentage of individuals covered for a given time period rather than CPT.

Board Ethics Assessment: LNX-003

Dr. Philpott stated that the protocol was ethically sound. He commended Ms. Sherman's identification of some minor deficiencies. The protocol adequately reflects Board input concerning how to improve the ethical conduct of such studies. The risks of the research are appropriately minimized and justified given the benefits the research poses to society and the risks have been clearly articulated. Concerns raised by EPA and Board members about stress to the participants have been satisfactorily addressed by Dr. Carroll. Management and risk minimization procedures detailed in this protocol are exceptional. Procedures to ensure voluntary and informed consent are adequate and subjects appear to be under no undue influence or coercion. Therefore, if modified as recommended by EPA, the study will meet the necessary ethical requirements. Dr. Menikoff agreed with Dr. Philpott's assessment. Dr. Philpott concluded that the consensus of the Board was that the study was ethically sound. He stated that he would create slides summarizing the Board's consensus and these will be placed on the HSRB docket.

Closing Remarks

Mr. Jordan thanked Dr. Philpott for serving as Chair and thanked the Board members for their thoughtful and helpful advice.

At this point, neither the AEATF-II nor AHETF have indicated that they will have new or completed protocols ready for review for the January 2010 Board meeting. In addition, EPA has not received requests for the Board to review insect repellent efficacy studies; therefore, the Board likely will not meet in January 2010.

Dr. Lewis thanked OSA and OPP for their efforts at the meeting. He said that his time working with the Board has been highly rewarding and educational. Through its thoughtful and thorough review of research involving human subjects, the Board has successfully provided greater protection to human subjects in the studies it has reviewed.

The meeting was adjourned by the Chair.

Respectfully submitted:

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

Certified to be true by:

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 and Consultants
Attachment B	Federal Register Notice Announcing Meeting
Attachment C	Meeting Agenda

Attachment A

EPA HUMAN STUDIES REVIEW BOARD MEMBERS

Chair

Sean Philpott, Ph.D., M.S. Bioethics
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Ernest D. Prentice, Ph.D.*
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Institute of Food and Agricultural Sciences
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* Not in attendance at the October 20-21, 2009 Meeting

Attachment B

Federal Register Notice Announcing Meeting

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

[Federal Register: October 2, 2009 (Volume 74, Number 190)]
[Notices]
[Page 50965-50967]
From the Federal Register Online via GPO Access [wais.access.gpo.gov]

ENVIRONMENTAL PROTECTION AGENCY
[EPA–HQ–ORD–2009–0658; FRL–8965–4]

Human Studies Review Board (HSRB); 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 from October 20–21, 2009, from approximately 10 a.m. to approximately 5:30 p.m., through October 20, 2009 from approximately 8:30 a.m. to approximately 12:30 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 Unit I.D. 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–2009–0658, 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–2009– 0658. EPA's policy is that all comments received will be included in the public docket without change and may be made available online at *http://www.regulations.gov,* including any personal information provided, unless the comment includes information claimed to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Do not submit information that you consider to be CBI or otherwise protected through *http://www.regulations.gov* or e-mail. The *http://www.regulations.gov* website 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 a.m. 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 October 2009. In addition, the Agency may provide additional background documents as the

materials become available. You may obtain electronic copies of these documents, and certain other related documents that might be available electronically, from the regulations.gov website and the 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**.

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

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

a. Explain your views as clearly as possible.

b. Describe any assumptions that you used.

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

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

e. To ensure proper receipt by EPA, be sure to identify the docket ID number assigned to this action in the subject line on the first page of your response. You may also provide the name, date, and **Federal Register** citation.

D. How May I Participate in This Meeting?

You may participate in this meeting by following the instructions in this section. To ensure proper receipt by EPA, it is imperative that you identify docket ID number EPA–HQ–ORD–2009–0658 in the subject line on the first page of your request.

a. Oral comments. Requests to present oral comments will be accepted up to October 13, 2009. To the extent that time permits, interested persons who have not pre-registered may be permitted by the Chair of the HSRB to present oral comments at the meeting. Each individual or group wishing to make brief oral comments to the HSRB is strongly advised to submit their request (preferably via e-mail) to the person listed under **FOR FURTHER INFORMATION CONTACT** no later than noon, Eastern time, October 13, 2009, in order to be included on the meeting agenda and to provide sufficient time for the HSRB Chair and HSRB Designated Federal Officer (DFO) to review the agenda to provide an appropriate public comment period. The request should identify the name of the individual making the presentation, the organization (if any) the individual will represent, and any requirements for audiovisual equipment (e.g., overhead projector, LCD projector, chalkboard). Oral comments before the HSRB are limited to five minutes per individual or organization. Please note that this limit applies to the cumulative time used by all individuals appearing either as part of, or on behalf of an organization. While it is our intent to hear a full range of oral comments on the science and ethics issues under discussion, it is not our intent to permit organizations to expand these time limitations by having numerous individuals sign up separately to speak on their behalf. If additional time is available, there may be flexibility in time for public comments. Each speaker should bring 25 copies of his or her comments and presentation slides for distribution to the HSRB at the meeting.

b. Written comments. Although you may submit written comments at any time, for the HSRB to have the best opportunity to review and consider your comments as it deliberates on its report, you should submit your comments at least five business days prior to the beginning of the meeting. If you submit comments after this date, those comments will be provided to the Board members, but you should recognize that the Board members may not have adequate time to consider those comments prior to making a decision. Thus, if you plan to submit written comments, the Agency strongly encourages you to submit such comments no later than noon, Eastern Time, October 13, 2009. You should submit your comments using the instructions in Unit I.C. of this notice. In addition, the Agency also requests that person(s) submitting comments directly to the docket also provide a copy of their comments to the person listed under **FOR FURTHER INFORMATION CONTACT.** There is no limit on the length of written comments for consideration by the HSRB.

E. Background

a. Topics for discussion. The HSRB is a Federal advisory committee operating in accordance with the Federal Advisory Committee Act (FACA) 5 U.S.C. App. 2 § 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 October 20–21, 2009, EPA's Human Studies Review Board will consider scientific and ethical issues surrounding three topics:

1. Completed, pre-rule research on the effects of exposure to pesticides containing pyrethrins/pyrethroids. EPA requests the advice of the HSRB on the scientific merit, relevancy, and limitations of these studies, and on their ethical acceptability. EPA intends to incorporate into a future revision of the EPA White Paper, "A Review of the Relationship between Pyrethrins, Pyrethroid Exposure and Asthma and Allergies," a discussion of either or both of these studies if they are deemed to be scientifically sound, relevant and ethically acceptable.

2. A proposal for new research to be conducted by Carroll-Loye Biological Research to evaluate in the laboratory the repellent efficacy to ticks of two registered products containing 20% picaridin. EPA requests the advice of the HSRB concerning whether, if it is revised as suggested in EPA's review and if it is performed as described, this research is likely to generate scientifically reliable data, useful for assessing the efficacy of the tested materials in repelling ticks, and to meet the applicable requirements of 40 CFR part 26, subparts K and L.

3. A new scenario design and associated protocol from the Antimicrobials Exposure Assessment Task Force II (AEATF–II), describing proposed research to monitor at three sites the dermal and inhalation exposure of professional janitorial workers who apply an antimicrobial pesticide formulated as an aerosol spray. EPA requests the advice of the HSRB concerning whether, if it is revised as suggested in EPA's review and if it is performed as described, this research is likely to generate scientifically reliable data, useful for assessing the exposure of those who apply antimicrobial pesticides as aerosols, and to meet the applicable requirements of 40 CFR part 26, subparts K and L.

In addition, the Board will be reviewing its draft June 24–25, 2009, meeting report for subsequent Board approval. Finally, the HSRB may also discuss planning for future HSRB meetings.

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

Dated: September 24, 2009.
Kevin Teichman,
EPA Acting Science Advisor.
[FR Doc. E9–23795 Filed 10–1–09; 8:45 am]
BILLING CODE 6560–50–P

Attachment C

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
HUMAN STUDIES REVIEW BOARD (HSRB)
OCTOBER 20-21, 2009*
PUBLIC MEETING

OCTOBER 20, 2009
Environmental Protection Agency
Conference Center – Lobby Level
One Potomac Yard (South Bldg.)
2777 S. Crystal Drive
Arlington, VA 22202

HSRB WEB SITE: http://www.epa.gov/osa/hsrb/
Docket Telephone: (202) 566-1752
Docket Number: EPA-HQ-ORD-2009-0658

- **10:30 AM** **Convene Meeting and Administrative Procedures** – Paul Lewis, Ph.D. (Designated Federal Officer [DFO], EPA Human Studies Review Board [HSRB], Office of the Science Advisor [OSA], EPA)
- **10:35 AM** **Introduction and Identification of Board Members** – Sean Philpott, Ph.D. (HSRB Chair)
- **10:45 AM** **Welcome** – Warren Lux, M.D. (Human Studies Research Review Official, OSA, EPA)
- **10:55 AM** **Opening Remarks** – Mr. Steve Owens (Assistant Administrator, Office of Prevention, Pesticides and Toxic Substances [OPPTS], EPA)
- **11:00 AM** **EPA Follow-up on Pesticide Specific HSRB Recommendations** – Mr. William Jordan (OPP, EPA)

Published reports of pyrethrins/pyrethroids research completed before enactment of EPA's expanded human studies rule (40 CFR part 26: Protection of Human Subjects)

- **11:05 AM** **EPA Science and Ethics Reviews** – Ms. Sarah Winfield (OPP, EPA), Ms. Carol Christensen (OPP, EPA) and Ms. Kelly Sherman (OPP, EPA)
- **11:55 PM** **Lunch**
- **1:00 PM** **EPA Science and Ethics Reviews (continued)**
  Board Questions of Clarification – Sean Philpott, Ph.D. (HSRB Chair) EPA -
- **1:30 PM** **Public Comments**
- **1:45 PM** **Board Discussion**

Newton & Breslin study (1983)

Is the Newton & Breslin study scientifically sound, providing reliable data?

If so, is the Newton & Breslin study relevant to an assessment of the proposition that exposures to pyrethrins/pyrethroids may be associated with asthmatic or allergic respiratory responses?

If so, what limitations of the Newton & Breslin study should be taken into account by EPA in assessing the proposition that exposures to pyrethrins/ pyrethroids may be associated with asthmatic or allergic respiratory responses?

Is there clear and convincing evidence that the conduct of the Newton & Breslin study was fundamentally unethical, or that its conduct was significantly deficient relative to standards prevailing when it was conducted?

Lisi study (1992)

Is the Lisi study scientifically sound, providing reliable data?

If so, is the Lisi study relevant to an assessment of the proposition that exposures to pyrethrins/pyrethroids may be associated with allergic contact dermatitis or sensitization responses?

If so, what limitations of the Lisi study should be taken into account by EPA in assessing the proposition that exposures to pyrethrins/pyrethroids may be associated with allergic contact dermatitis or sensitization responses?

Is there clear and convincing evidence that the conduct of the Lisi study was fundamentally unethical, or significantly deficient relative to the standards of ethical research conduct prevailing when it was conducted?

- **3:00 PM** **Break**
- **3:15 PM** **Draft Summary of Board Conclusions –** Sean Philpott, Ph.D. (HSRB Chair)

Proposed AEATF-II research on exposure of janitorial workers applying antimicrobial pesticides formulated as aerosol sprays (Protocol AEA04)

- **3:30 PM** **EPA Science and Ethics Reviews** – Mr. John Carley (OPP, EPA), Mr. Timothy Leighton (OPP, EPA), Cassi Walls, Ph.D. (OPP, EPA) and Ms. Kelly Sherman (OPP, EPA)
  Board Questions of Clarification – Sean Philpott, Ph.D. (HSRB Chair)
  EPA -
  Principal investigator/sponsor –
- **4:45 PM** **Public Comments**
- **5:00 PM** **Board Discussion**

If the proposed AEATF-II aerosol application scenario and field study protocol AEA04 is revised as suggested in EPA's review and if the research is performed as described:

1. Is the research likely to generate scientifically reliable data, useful for assessing the exposure of handlers who apply antimicrobial pesticides formulated as aerosol sprays?

2. Is the research likely to meet the applicable requirements of 40 CFR part 26, subparts K and L?

- **6:00 PM** **Adjournment** – Sean Philpott, Ph.D. (HSRB Chair) and Paul Lewis, Ph.D. (HSRB DFO)

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
HUMAN STUDIES REVIEW BOARD (HSRB)
OCTOBER 20-21, 2009*
PUBLIC MEETING

OCTOBER 21, 2009
Environmental Protection Agency
Conference Center – Lobby Level
One Potomac Yard (South Bldg.)
2777 S. Crystal Drive
Arlington, VA 22202

- **8:30 AM** **Opening of Meeting** – Paul Lewis, Ph.D. (HSRB DFO)
- **8:35 AM** **Introduction** – Sean Philpott, Ph.D. (HSRB Chair)
- **8:40 AM** **Follow-up from Previous Day** – Mr. William Jordan (OPP, EPA)

Proposed AEATF-II research on exposure of janitorial workers applying antimicrobial pesticides formulated as aerosol sprays (Protocol AEA04)

- **8:45 AM** **Draft Summary of Board Conclusions** – Sean Philpott, Ph.D. (HSRB Chair)

Review of June 24-25, 2009 HSRB Meeting Report
- **9:00 AM** **Review Process** – Sean Philpott, Ph.D. (HSRB Chair)
- **9:05 AM** **Public Comments**
- **9:15 AM** **Board Discussion and Decision on Report** – Sean Philpott, Ph.D. (HSRB Chair)
- **10:00 AM** **Break**

Proposed Carroll-Loye Biological Research, Inc. Study (LNX-003): Efficacy of Two Picaridin-Based Personal Insect Repellent Formulations against Ticks
- **10:15 AM** **EPA Science and Ethics Reviews** – Mr. Kevin Sweeney (OPP, EPA) and Ms. Kelly Sherman (OPP, EPA)
  Board Questions of Clarification – Sean Philpott, Ph.D. (HSRB Chair)
  EPA –
  Principal investigator/sponsor –
- **11:15 AM** **Public Comments**
- **11:30 AM** **Board Discussion**

If the proposed laboratory tick repellency study protocol LNX-003 is revised as suggested in EPA's review and if the research is performed as described:

1. Is the research likely to generate scientifically reliable data, useful for assessing the efficacy of the tested materials in repelling ticks?

2. Is the research likely to meet the applicable requirements of 40 CFR part 26, subparts K and L?

- **12:30 PM** **Break**
- **12:45 PM** **Draft Summary of Board Conclusions –** Sean Philpott, Ph.D. (HSRB Chair)
- **1:00 PM** **Adjournment** – Sean Philpott, Ph.D. (HSRB Chair) and Paul Lewis, Ph.D. (HSRB DFO)

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