January 2, 2008

Minutes of the
United States Environmental Protection Agency (EPA)
Human Studies Review Board (HSRB)
October 24-26, 2007 Public Meeting
Docket Number: EPA-HQ-ORD-2007-0942
HSRB Web Site: http://www.epa.gov/osa/hsrb/

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

Dates and Times: Wednesday, October 24, 2007, 8:30 AM – 3:30 PM
Thursday, October 25, 2007, 8:00 AM – 6:45 PM
Friday, October 26, 2007, 8:30 AM – 12:30 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 (HSRB or Board) provides advice, information, and recommendations on issues related to the scientific and ethical aspects of human subjects research.

Attendees:

Chair:	Celia B. Fisher, Ph.D.
Vice Chair:	William S. Brimijoin, Ph.D.
Board Members:	Gary L. Chadwick, PharmD, MPH, CIP
	Janice Chambers, Ph.D., D.A.B.T.
	Susan S. Fish, PharmD, MPH
	Suzanne C. Fitzpatrick, Ph.D., D.A.B.T.
	Dallas Johnson, Ph.D.
	KyungMann Kim, Ph.D., CCRP
	Kannan Krishnan, Ph.D.
	Michael D. Lebowitz, Ph.D., FCCP
	Lois D. Lehman-Mckeeman, Ph.D.
	Jerry A. Menikoff, M.D.
	Rebecca Parkin, Ph.D., MPH
	Sean M. Philpott, Ph.D.
	Richard Sharp, Ph.D.

Meeting Summary: Meeting discussions generally followed the issues and general timing as presented in the meeting agenda (Attachment C), unless noted otherwise in these minutes.

Introduction and Identification of Board Members

Dr. Celia Fisher (Chair, HSRB) opened the meeting and welcomed Board members, U.S. Environmental Protection Agency (EPA or Agency) staff, and members of the public to the October 2007 HSRB meeting. She acknowledged the efforts of Dr. Paul Lewis (Designated Federal Officer [DFO], HSRB, Office of the Science Advisor [OSA], EPA) and members of EPA's Office of Pesticide Programs (OPP) in planning and preparing for this meeting. She introduced the Board consultants who were participating in the meeting. Dr. Germaine Buck Louis (HSRB Consultant) is a researcher in the Division of Epidemiology, Statistics and Prevention Research, National Institute of Children and Human Development. Dr. P. Barry Ryan (HSRB Consultant) works for the Department of Environmental and Occupational Health, Rollins School of Public Health, Emory University. Dr. Fisher also introduced two new Board members, Dr. Dallas Johnson who is Professor Emeritus at Kansas State University and Dr. Rebecca Parkin, Associate Dean for Research and Public Health Practice, School of Public Health and Health Services, The George Washington University. At Dr. Fisher's request, Board members introduced themselves. Dr. Fisher thanked Dr. Brimijoin, Vice Chair, for the excellent job he performed chairing the June meeting.

Welcoming Remarks

Dr. George Gray (Science Advisor, EPA) welcomed Board members and conveyed EPA's appreciation for their work in preparing for and participating in the HSRB meetings. He also thanked EPA staff for their efforts in preparing for this meeting. He welcomed the two new Board members, and expressed his thanks to Dr. David Bellinger, who has resigned from the Board.

Dr. Gray noted that this meeting marked one and a half years since the Board began review of third-party intentional dosing experiments in humans for use by EPA's Office of Pesticide Programs. He described a new topic for the day's discussion, which is an effort on the part of EPA's Office of Research Development (ORD) to prepare a resource tool to assist investigators in considering the science and ethics of human observational exposure studies. Dr. Kevin Teichman (Acting Associate Director for Science, Office of Research and Development) stated his interest in the Board's perspective and advice concerning such experiments to ensure that this research is performed following the most current considerations of science and ethics. EPA's National Exposure Research Laboratory (NERL) is a leader in performing exposure assessments in the community to gather data for EPA's exposure assessment portfolio.

The Agency seeks to develop a framework for issues researchers should consider as they plan and implement observational exposure studies. The framework is intended to serve as a reference document, not an official guidance document. In the future, the HSRB may have an opportunity to examine proposed and completed human exposure studies with respect to the established framework.

Dr. Debbie Edwards (Director, OPP, EPA) welcomed participants and Board members to the 8th meeting of the HSRB. She noted that a variety of topics would be discussed at this

meeting, including the proposed framework for observational exposure studies, new protocols and completed studies of insect repellent efficacy, science issues in mosquito repellent efficacy field research, and assessment of exposure to sodium azide. She expressed her appreciation of the time and effort on the part of the Board and EPA staff for preparing for this meeting and drafting the final report. She thanked Dr. Lewis and Ms. Crystal Rodgers-Jenkins (OSA, EPA) specifically for their help with preparing for this meeting.

Meeting Administrative Procedures

Dr. Lewis welcomed Board members and thanked them and his EPA colleagues for their efforts in preparing for this meeting and also welcomed members of the public. As the DFO, Dr. Lewis serves as liaison between the HSRB and EPA and ensures that Federal Advisory Committee Act 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 five minutes.

He acknowledged Drs. Ryan and Buck Louis who have been asked to provide specialized information on topics presented at the October 24, 2007 session. The HSRB consultants do not participate in the Board decision-making process.

EPA Follow-up on HSRB Recommendations

Mr. William Jordan (OPP, EPA) reviewed EPA follow-up on HSRB recommendations from the June 2007 HSRB meeting. Topics reviewed at the June 2007 meeting included the Carroll-Loye Picaridin Mosquito Repellency Protocol LNX-001, the ICR Picaridin Mosquito Repellency Protocol A044, the completed Inhalation Toxicity Study on Acrolein and Clinical Studies on 4 Amino-Pyridine (4-AP), and Science and Ethics Issues for Handler Research. Regarding the protocol LNX-001, the Board concurred with EPA's conclusion that the studies "are sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy" of the tested products and also with EPA's conclusions that the studies met applicable standards of EPA's human studies regulation. As of the October 2007 HSRB meeting, Dr. Scott Carroll (Carroll-Loye Biological Research, Inc**.**) had not initiated this research; EPA will review any study report concerning this research once it is submitted by Dr. Carroll.

Regarding the ICR protocol A044, the Board recommended several changes, including using "first confirmed landing with intent to bite (FCLIBe)" as evidence of efficacy failure, serology testing on aspirated mosquitoes to detect disease-causing pathogens, provision of an explanation of the statistical analysis plan, and inclusion of a dosimetry study. If revised to accommodate these changes, the protocol should produce scientifically reliable data. The Board concurred with EPA's assessment that the submitted protocol would not meet the applicable requirements of EPA's human studies rule and recommended changes to make it compliant. In

response, ICR submitted a revised protocol A044; EPA determined that further revisions were necessary to address EPA's and the Board's recommendations. Subsequently, ICR has informed EPA that the sponsor has decided not to pursue this research.

Regarding the completed Inhalation Toxicity Study on Acrolein, the Board determined that the Weber-Tschopp inhalation toxicity study was sufficiently scientifically sound to be used to estimate a safe level of acute inhalation exposure to acrolein. The majority of the Board concluded that there was not clear and convincing evidence that this study was fundamentally unethical or significantly deficient relative to the ethical standards prevailing when the study was conducted, despite a lack of information and some slightly troubling aspects of the report. Dr. Michael Lebowitz provided valuable background information that helped the Board draw its conclusions. Based on the Board's assessment, EPA used the results of the Weber-Tschopp inhalation toxicity study as a basis for estimating a safe level of acute inhalation exposure to acrolein.

Regarding the completed Clinical Studies on 4-AP, the Board concluded that these studies were sufficiently scientifically sound to be used to derive a point of departure (POD) for estimating risk to humans. The HSRB also concurred with EPA's conclusion that there was not clear and convincing evidence that the studies were fundamentally unethical or significantly deficient with respect to ethical standards prevailing when the studies were conducted. Consequently, EPA has relied on the results of the three 4-AP studies to evaluate the potential human risk of exposure to this chemical.

The Board also discussed governing documents provided by the handler exposure task forces and concluded that these documents adequately addressed both the potential risks and benefits of the proposed research. EPA agrees with the Board's conclusions and will work with the task forces to clarify the discussions of risks and benefits for specific exposure scenarios. The HSRB also recommended that EPA consider the need for data on the efficiency of residue removal procedures, particularly for body parts not covered by the passive dosimetry garments (i.e., hand washes and face/neck wipes). EPA has decided to review the results from specific completed exposure studies to determine, on a study-by-study basis, the need for data on the efficiency of residue removal procedures and the need for corrections of exposure estimates. The Board agreed with EPA's conclusion that handler research should rely on passive dosimetry methods and should not routinely include concurrent biomonitoring. The HSRB found the task forces' Standard Operating Procedures (SOPs) to be "reasonably complete" but recommended adding SOPs to address data quality, sample integrity, and protocol compliance. The task forces have indicated to EPA that they expect to add such SOPs.

Regarding sampling, the HSRB recommended that the task forces collect data on "within worker" variability to permit estimation of the "usual exposure" at the high end of the distribution of individual exposures. By "usual exposure," the HSRB means the distribution of the means of workers' multi-day exposures across the handler population. EPA understands and agrees with the Board's conclusion that measures of "within worker" variability are necessary to assess "usual exposure," but believes that it does not require such information to assess the risks associated with multi-day exposures. Therefore, EPA has advised the Task Forces to collect

monitoring data from a maximum number of different individual subjects in order to best characterize between-worker variability.

In general, the Board favorably reviewed the Task Forces' approaches to recruiting and enrolling subjects, and recommended a few improvements. EPA will work with the Task Forces to address these recommendations. The Board discussed in detail the task forces' proposals to use "purposive diversity sampling" strategies and recommended consideration of randomized sampling strategies. EPA will provide an update of this topic later during the meeting.

Clarifying Questions

Dr. Johnson asked Mr. Jordan to define the term point of departure "POD." Mr. Jordan explained that EPA's approach to assessing risk associated with exposure to pesticides begins with identification of the types of hazards and adverse effects of exposure to a particular pesticide. For most pesticides, this depends on data obtained primarily from animal toxicity studies. From these data, the first effect occurring as a consequence of exposure and the dose level at which the effect occurs are identified. If the first effect does not occur, the dose is low enough to ensure that subsequent effects will not occur; this is the "point of departure (POD)." After the POD is determined, EPA applies uncertainty factors (10x) to account for higher human sensitivity to the pesticide's effects compared to animals. Another 10-fold uncertainty factor is applied to ensure protection of the most sensitive sub-populations. A further 10-fold uncertainty factor is applied to account for possible uncertainties regarding the sensitivity of children or those with unusual exposure profiles for the pesticide. The goal of this exercise is to ensure that humans are not exposed to a level greater than one thousandth of the toxic value associated with the first toxic endpoint; that toxic endpoint is the POD. Human toxicity data are used similarly, but uncertainty factors are applied differently.

Scientific and Ethical Approaches for Observational Exposure Studies (SEAOES)

Introduction

Dr. Fisher commended Dr. Larry Cupitt (Senior Science Advisor, NERL, ORD, EPA) and Dr. Roy Fortman (ORD, EPA) on the thoroughness and clarity of the Scientific and Ethical Approaches for Observational Exposure Studies (SEAOES) document. Dr. Gray explained that the HSRB was the preferred group to review this document because of the variety of expertise and scientific and ethics perspectives of Board members. He thanked the Board for agreeing to review the document.

Dr. Cupitt presented an overview of the SEAOES document. EPA's mission is to develop regulations that protect public health. The Agency uses risk assessments to identify and characterize environmentally related health problems and uses this information for risk management purposes. Understanding and quantifying exposure and how it occurs is critical to the risk assessment process. The SEAOES document was developed to serve as a resource for NERL researchers. The document identifies important scientific and ethical issues researchers should consider during the design and implementation of observational exposure studies. The document will provide resources and references for NERL researchers as they design protocols

involving human subjects, ensure that the science is of the highest quality and that ethical standards are understood and upheld at the highest possible level. A focus on ethical standards is particularly important because NERL research often involves observations in people's homes.

NERL scientists and managers take protection of the privacy and integrity of research participants seriously, and wish to meet both the regulatory requirements and the spirit of the ethical standards that motivate regulatory requirements. Exposure studies have impacted people's lives; understanding exposure has led to actions by EPA and other agencies that have resulted in protection of human health and the environment. Examples of studies that have led to regulatory actions to protect human health include studies of exposure to particulate matter (PM2.5), volatile organic compounds, radon, and formaldehyde.

Exposure is defined as the contact of an individual with a chemical or pollutant through breathing, eating, drinking, or touching surfaces. Understanding and characterizing exposure requires understanding the concentrations of a chemical in people's environments and observing the human activities that bring people in contact with the chemicals. To understand the impact of these activities on human health requires data collected through observational human exposure studies. The data contribute to the development of uncertainty factors, which are important for risk management activities; the risk management activities can include changing a source of exposure or a means of contact, which could decrease potential exposure and risk.

Observational human exposure studies involve observation and measurement of people's contact with chemicals that are already present in their environment under real-world conditions (such as in homes, offices, cars, and the outdoors) and during normal day-to-day activities. These studies collect a variety of samples including air (from indoor, outdoor, and personal sampling); food, water, and beverages; dust; soil; and biological samples including urine and blood; hand wipes and surface residue transfer studies will also be conducted. These samples contribute to research to understand the distribution of chemicals in the environment, the range of chemicals in contact with individuals, and the activities that bring people into contact with the chemicals. Other data collected in these studies include time/activity information, personal activities, product use, diet, occupation, and housing characteristics.

NERL researchers identify populations in need of exposure assessment. Exposure studies are performed where the populations live through field studies. NERL researchers have developed data collection tools to collect samples, detect pollutants at low concentrations, and also perform appropriate statistical analyses. The goal of these studies is to help communities and regions assess human health risk and determine the impact of exposures. NERL researchers study locations where people spend significant portions of time. Samples are collected from floors, surfaces, toys, and by vacuuming to collect dust samples; many of these activities focus on areas often contacted by children. Personal samples are obtained using cotton garments, duplicate diet plates (to assess exposure from dietary sources), urine samples, and time-activity diaries.

NERL requested the Board provide comments on the SEAOES document. The document was developed through stakeholder conversations and convening of an expert panel workshop, held November 28-29, 2006. An internal review of the document by program offices and

scientists within ORD and EPA Regions was performed. A public comment period began on October 4, 2007, and will continue until November 19, 2007. The goal is to have the final document revised and published in early 2008. The Board was asked to consider whether each section of the document identifies the major scientific and ethical issues that need to be addressed; these issues overlap with scientific considerations. The Board also was asked to identify any additional sources of information that should be considered for inclusion in the sections, and whether the information contained in the document is presented accurately and clearly in each section.

The SEAOES document begins by describing observational human exposure studies. The introduction presents ethical issues arising in human observational exposure studies, the purpose of the document, process for developing the document, and its organization. Section 2 describes elements to be considered in study conceptualization and planning, including defining the study problem and justifying a human exposure study. The section also describes planning and scoping activities, and presents innovative and alternative study designs and ways to assess benefits and risk for participants. These activities lead to development of a study design and human studies protocol that are scientifically sound and meet applicable ethics requirements. Human observational exposure studies are subject to scientific and ethical review; the document establishes criteria for data and safety monitoring of scientific and ethical issues. Procedures for implementing and monitoring these studies also are described.

Section 3 describes ways to ensure protection of vulnerable groups. Vulnerable groups are identified and justification for involving or excluding vulnerable groups is addressed. This section includes specific discussions of research involving children, women, and other potentially vulnerable groups. Section 4 addresses privacy, confidentiality, and other concerns related to observational human exposure studies. Privacy issues are a primary concern because these studies involve researchers entering participants' homes; participants have volunteered for this research, but the research activities nonetheless could constitute an invasion of privacy. The document addresses issues pertaining to confidentiality of information and participation that arise from entering participants' homes. This section also describes collateral observations and reporting of hazards in the homes that are not part of the study. The section familiarizes researchers with potential non-study hazards, reporting requirements, hazard communication, planning, and staff training. These studies also may impact third parties, such as a landlord if the study participant is a renter. This section also describes appropriate data and safety monitoring and oversight.

Section 5 provides recommendations on creating an appropriate relationship between the participant and the researchers. The "three pillars" of the informed consent process—information, comprehension, and voluntary participation—are discussed. This section addresses the sometimes controversial issue of payments to research participants, research rights and grievance procedures, how to create a supportive environment, recruitment strategies, and retention strategies. This section clearly emphasizes the importance of communication. Section 6 provides suggestions for building and maintaining appropriate community and stakeholder relationships. The section discusses ways to define the "community," identifying who represents the community, building relationships and trust, use of community advisory boards, engagement of the community throughout the study, and identifying and interacting with

other stakeholders. Section 7 addresses communication from the perspective of the researcher. This section provides advice for the design and implementation of strategies for effective communication. It addresses issues, such as identifying the individuals and groups involved in the communications, design of appropriate communication materials, and education of the participants and the community. This part of the document also suggests ways to report results to the participants and the community, how to report unanticipated results or observations, how to anticipate and respond to criticisms, and how to respond to media, public inquiries, and stakeholders.

The overarching goal of this document is to demonstrate the importance of observational human exposure studies to EPA's efforts to reduce risks and protect human health. Such studies help determine the chemicals people come into contact with, the concentration of the chemicals, the most important sources, pathways, and routes of exposure, and how, when, where, and how often people come into contact with these chemicals. The protection of research participants is taken seriously by NERL researchers and this document is designed to ensure that regulatory requirements, as well as the ethical standards that motivate those requirements, are met.

Clarifying Questions

Dr. Lebowitz inquired how information gathered from these studies is used within EPA and ORD offices, particularly for developing policy, goals, recommendations, and guidelines. He also requested clarification of how to definitively separate observation from other activities and the difference between observational and intentional exposure. Dr. Cupitt referred Dr. Lebowitz to regulation 40 CFR 26 which describes "intentional" exposure; all other exposures are observational. Ultimately, the decision for defining exposure as intentional or observational within the meaning of the regulations rests with Dr. Warren Lux (Human Subjects Research Review Official, OSA, EPA). Dr. Lux stated that it is important for the Board to distinguish between the regulatory definition of observational and their own intuitive ideas of what observational means. NERL is attempting to align its definition with the intuitive idea of observational exposure, yet ensure that this definition agrees with the regulatory definition. Intentional exposure is defined as the introduction of a substance by the researcher and study of that substance. Ambient exposures that normally occur but are specifically controlled constitute intentional exposure. If the substance being studied is not introduced or controlled, such an experiment meets the regulatory definition of "observational." Mr. Jordan further clarified that intentional exposure includes study of a substance in which exposure of the subject to the substance would not have occurred but for participation in the study. Although wiping hands with an alcohol wipe constitutes exposure to the alcohol, the alcohol is not the substance being studied, thus, the exposure is observational. In general, if the researcher determines that a subject will be exposed to a specific substance, this constitutes intentional exposure. For the handler exposure studies, EPA will consider whether a subject has made all decisions regarding exposure and what influences his exposure. If the decisions lie completely with the subject, the study is an observational exposure study. If the researchers are scripting the behavior (such as determining the amount or type of pesticide or antimicrobial the subject will use), this constitutes intentional exposure.

Dr. Fisher questioned how a home observational study would be interpreted if a researcher gives the participants an EPA-registered product or formulation, but the participant decides how to use the product. Dr. Cupitt answered that such a scenario has not arisen. Dr. Roy Fortmann (ORD, EPA) added that EPA observational studies do not provide products or ask participants to use a particular product. For NERL, observational means there has been no attempt to change the behavior or environment of the participants. The SEAOES document is limited to NERL observational studies. Dr. Lux agreed that a study in which a family is given a particular substance to use would be defined as an intentional exposure study because the researcher is introducing into the research a substance that otherwise would not be present in the family's environment. Observational studies in which exposure is altered without changing the participants' behavior, such as using a filter to reduce exposure, are considered to be observational because no foreign substance has been introduced.

Dr. Susan Fish requested clarification on the difference between research planning and scoping. Dr. Fortmann explained that scoping involves determining the size of the study and other practical issues related to the study environment and conceptualization of what is needed to address the research questions; planning is more detailed than scoping. Dr. Lebowitz commented that conceptualization is important because of specific environmental issues or concerns and should be performed prior to focusing on the goals and objectives of the research. Scoping could be considered a practical aspect of planning. Scoping also involves determining activities taking place after the data and results are collected, such as communicating the results to the scientific community. Intra-agency interests may influence scoping that occurs before goals and objectives are defined.

Dr. Cupitt clarified scoping as determining overall objectives for the research, such as determining all paths for exposure, which would have the least information or the most relevance, or routes resulting in the highest or most likely exposure. Planning involves how to conduct the research to gather the necessary information.

Dr. Kannan Krishnan asked for further clarification of the definition of intentional versus observational exposures. He specifically inquired about subject manipulation particularly with respect to blood draws, which are invasive procedures, and asked whether performing invasive sampling would result in defining the study as intentional exposure. Dr. Lux explained that a study that includes invasive sampling procedures can nonetheless be defined as observational as long as the researcher does not create exposure to a substance that would not otherwise have occurred. "Invasive" is not equivalent to "not observational." Dr. Fish commended Dr. Lux's clarification of observational studies and added that regulations speak only to introduction of a specific chemical. Observational studies do not waive ethical issues pertaining to sample collection, such as blood draws or increased risk of heat injury when subjects wear passive dosimetry garments. Dr. Lux added that manipulation of participants' behaviors can constitute an intentional exposure study. EPA considers this, and if a subject is exposed to a substance they are not normally exposed to because of behavior changes specified by the study, the study is considered intentional exposure, even if the researcher did not introduce a specific substance. Dr. Fisher asked Dr. Lux to clarify whether reduction of exposure would permit the study to be considered observational. Dr. Lux explained that he would consider a study including mitigation of an exposure that would normally occur to be observational.

Dr. Fisher noted that the Board evaluates third-party research and described a situation in which a substance introduced for clinical trial purposes has information that could be used by EPA. She asked whether such a study would be considered observational or intentional exposure. Dr. Lux explained that the regulations do not distinguish among different types of substances (i.e., toxic or therapeutic). Introduction of any substance constitutes intentional exposure. He agreed that such a situation could lead to unintended consequences regarding research that is or is not permitted to be used by EPA and added that this issue would be addressed in the future. Dr. Fisher questioned whether data from trials in which children participated could be used by EPA. Dr. Lux responded that depending on the circumstances of the trial, such data might be legitimate to use.

Dr. Suzanne Fitzpatrick inquired about the number of studies performed by NERL and how such studies were prioritized. She also asked how compliance is ensured within studies performed using Cooperative Research and Development Agreements. Dr. Cupitt explained that NERL performs a small number of studies, perhaps one per year. He described as an example a study of air exposure in adults performed in Detroit, Michigan. This study took place over three years, beginning with sampling and continuing through analysis. The study examined how a particular chemical was distributed in the environment and how people came into contact with it. No children have been involved in NERL exposure studies for the past few years. Dr. Cupitt also noted that Section 2 of the SEAOES document discusses NERL priorities. Based on funding and the needs of program offices within EPA, studies are designed to address identified weaknesses in EPA's portfolio. Dr. Cupitt explained that ORD does not have sponsors perform this exposure research. Mr. Jordan clarified that OPP is unusual in its ability to require companies to generate data to support registration of pesticide products. ORD has no regulatory authority.

Dr. Lebowitz noted that the document does not address ORD interactions with other groups or studies funded by second parties; however, the information collected by ORD is used for regulatory purposes. Dr. Cupitt explained that NERL collaborates with academic researchers. The document is also intended to serve as a resource tool for researchers to rely on as they develop and conduct observational human exposure studies.

Dr. Fisher clarified that intentional exposure research involves introduction of a substance that participants would not otherwise be exposed to and introduction of the substance by researchers. She asked if providing participants with a substance that they normally use would constitute intentional exposure. Dr. Lux responded that if the researchers ask the participants to use a substance as a condition of participation, the study involves intentional exposure. Dr. Fisher noted that if a third party conducts an observational study, risks and benefits must be evaluated according to regulations. Third parties do not have to submit observational studies before implementation, but do have to submit intentional exposure studies. She asked whether ethical review of third-party observational research is performed to assess whether EPA can use the results of the research. Dr. Lux explained that all such research requires Institutional Review Board (IRB) review. Mr. Jordan added that OPP will review the results of observational research submitted by third parties for registration purposes. Dr. Fisher inquired whether EPA would decline to use data from research that was sound, but was not

conducted in conformance to ethical standards. Mr. Jordan answered that EPA might decline to use such data.

Board Discussion

Dr. Steven Brimijoin opened discussion of the SEAOES document by commending the authors on the clarity and organization of the document. The Introduction was organized in a straightforward manner, met its stated goals, and provided an outline of the approach used in each section. The use of the term "scoping" should be reconsidered to define these activities more clearly for investigators who do not work within NERL. The Introduction defines the scope of research as pertaining to observational studies and defines observational exposure; the difference between observational and intentional exposure research might require more clarification, especially for investigators outside of NERL. Dr. Brimijoin commended Dr. Lux for his explanation of the concept of ordinary use of the term "observational" as compared to the regulatory use. Observational does not equal benign; therefore, observational studies could still be considered to be unethical even if they meet the definition of "observational."

Dr. Brimijoin suggested adding a paragraph to include Dr. Lux's observational versus intentional exposure explanation. He also suggested adding a text box containing examples. For example, the Agricultural Handlers Exposure Task Force (AHETF) research will be treated as intentional exposure research because of the inclusion of scripted activities, changing exposure, and using similar but not the same chemicals that handlers normally would use. Such an explanation would be valuable for third-party investigators. He reiterated that the document is not intended to be coercive, but rather will offer guidance and assistance to investigators.

Dr. Gary Chadwick reviewed Section 1 of the SEAOES document. He noted that the document was well-written and a comprehensive yet succinct description of the content; background was provided throughout the document. The document contains references to a number of publications and attempts to summarize these and include key points, such as in Table I-4. This summarization appears to be lacking in other sections and including this would strengthen the document. The document addresses major areas of concern, but to some extent ignores the science; the document should acknowledge how science and ethics complement one another. An assumption is made that good science and good ethics interact, but this may not be clear to new investigators. Throughout the document, references are made in a style more appropriate to a journal article than to a guiding document. The document should take ownership of EPA decisions rather than summarizing what was found. For example, on page 10, lines 1-3, a wording change to indicate "We have recommended…" would strengthen the document.

Dr. Parkin noted that the abstract states that the document will address chemicals and other stressors, but focuses on chemicals, which gives the impression that guidance is not needed except for research involving chemicals. The language and examples used in the document should reflect the importance of the document for both chemicals and other stressors.
Dr. Krishnan reemphasized the importance of expanding on the definition of observational research. Section 1 begins with a lay definition and provides a regulatory definition as a footnote.

The regulatory definition should be placed in the main text and issues arising in today's discussion should be included.

Dr. Fish opened discussion of Section 2. She recommended that the term "conceptualizing" replace "scoping," particularly if the document is intended for use outside of NERL. She expressed concern with Figure 2-1, which appears to separate the study design document from the human subjects protocol document. The text explains that these are overlapping documents. Describing two documents in the figure could lead to inconsistencies and she cautioned against having two different descriptions. Concerning Text Box 2-1, describing elements to be considered in justifying studies, the third bullet should include discussion of alternative designs or models to help justify the use of human subjects. She suggested that Section 2.1.1, entitled, "Innovative Study Designs" needs to be re-titled or the content redesigned because it speaks more to adding direct benefits for the participant to the research protocol when the benefits do not affect the protocol, for example, providing teaching tools. This is good practice, but is not an "innovative study design."

Section 2.2.4 relates to conflict of interest. A statement herein refers to many sources of conflict of interest, but also states that those related to funding are the most likely to occur. Dr. Fish noted that in her experience, in academic settings conflicts of interest related to project funding are the easiest to identify, but conflicts of interest related to promotion are much more difficult to identify and reduce. Text Box 2-3 describes elements to include in a study design; material describing precision or accuracy for measurement of environmental conditions, factors, or endpoints needs to be added. References to survey design and instruments should include whether the instruments are validated or require validation. She referred to two recent articles published in *Public Library of Science Medicine* that related to strengthening reporting of observation studies which contained lists of items to include. Tables in these articles may be useful to this section of the SEAOES document and should be referenced.

Section 2.3.1.1 discussed determining sample size but claimed that only a small amount of literature on sample size determination is available; this is untrue and should be corrected. Text Box 2-5 discusses potential topics for human research protocols. Each IRB has its own forms and requirements; the text box listed "best practices" beyond what a single IRB might require. Regarding item 22, "adverse events" should be changed to "unanticipated problems affecting subjects and others," which aligns with the language contained in regulations and is broader than adverse events. Dr. Brimijoin suggested that both terms be included. For item 34, inclusion of future unforeseen or unplanned use of data and biologics material should be considered. For item 42, procedures for presenting instances of falsification of data should be included.

Dr. Lebowitz agreed that Section 2 was strong, particularly considering overall concepts of study planning and ethics considerations. General areas of deficiency given the purpose of the document include a lack of information and materials concerning observational studies, more balance between science and ethical issues, and specific problems relevant to observational exposures studies. A specific description of exposure studies protocols is lacking. Excellent sources of this information are available, for example through the World Health Organization (WHO) and OPP. A 1991 National Academy of Sciences (NAS) report on human exposure

assessment is available, as well as a WHO series on environmental epidemiology. Dr. Lebowitz noted that Section 2.2.1 does not define types of study questions scientifically nor does it provide references. Ethics discussions in Section 2.2.2 provide no basis or criteria for the scientific component or specific references. Section 2.2 lacks an outline of the steps and planning involved in observational exposure research and does not state where such information could be found. Text Box 2-2 delineates the components of a study relevant to planning. Section 2.2.3 lacks details concerning the scope of scientific planning. Section 2.3.1 does not include important or appropriate questions regarding scientific feasibility or measurement information. Section 2.3.1.1 provides insufficient descriptions of sample size, and also lacks descriptions of actions to take in the case of participation refusal or loss, inter- and intra-observer variability, participant reporting biases, or inappropriate or inadequate reporting criteria. In response to the charge questions, Section 2 identifies major areas and issues where ethics should be addressed. Additional sources of information should be considered for inclusion. Section 2 is insufficient from a scientific perspective as a source of information for investigators to plan and design observational exposure studies. There are specific examples, including completed NERL studies that should be incorporated, rather than merely referenced. Descriptions of measurement methods should include new patch dosimetry methods and passive dosimetry for dermal exposure; it is important to show that exposure assessment practices continue to be developed.

Dr. Johnson noted that Section 2 was missing descriptions of participants and sampling units. The document needs to address ethical ways to select participants. Bad science is unethical, and a primary criterion for good science is to ensure that the participants are representative of the population to which the observations will be extended. Dr. Fitzpatrick asked whether NERL has other guidance documents that provide more of the "how to" for the science, which may explain why this was lacking in the SEAOES document. Dr. Cupitt responded that NERL chose to focus the document and receive input on areas where it has less expertise. Dr. Fitzpatrick remarked that if NERL has SOPs for its research, leaving these specifics out of the SEAOES document is acceptable. She commented that regarding unforeseen uses of data, under the Health Insurance Portability and Accountability Act (HIPAA), data cannot be used for activities not defined in the research protocol. Dr. Fisher and Dr. Fish commented that HIPAA only applied when data was protected health information (PHI) that would be used for a patient's treatment, health insurance, or billing by a "covered entity" and that the majority if not all of the NERL research would not fall under HIPAA. Dr. Fitzpatrick asked Dr. Lux if researchers were required to have a concept review performed by him. Dr. Lux explained that a formal mechanism for this process does not yet exist.

Dr. KyungMann Kim noted that observational studies can be considered to be survey sampling, but there is no reference to this in the document. Sample size calculations and references that are included in the document are incorrect for survey-type studies. The National Centers for Health Statistics has relevant information.

Dr. Fisher inquired about actions investigators would take if an unanticipated high concentration of a toxic substance was found in the course of an observational study. Dr. Fish explained that a health alert would be issued. Dr. Fisher suggested providing an example of such a situation in the section related to communication issues. Dr. Cupitt noted that this also could be relevant to Section 2.7, which discusses standards for monitoring. This situation was not

anticipated by NERL, but a process to determine appropriate actions if such a situation arises is needed. Dr. Richard Sharp noted that a plan is needed to address other types of "adverse events" that could occur during observational studies, such as an attack on a researcher who asks questions that are perceived as objectionable by a participant. Dr. Cupitt explained that Section 7.8 discusses reporting elevated concentrations of substances, procedures for ascertaining levels, and procedures for reporting participants. Addressing collateral observations and reporting standards are discussed in different sections, although these issues cut across all sections.

Dr. Fisher summarized Board discussion of Sections 1 and 2. Overall, the document is well written. The document is intended to provide internal as well as external educational value. A clearer definition of "scoping" would be helpful. Suggestions were made to increase the clarity of the definition of "observational" for regulatory purposes versus "intuitive" notions of such research and provide the type of examples that differentiate observational from intentional exposure studies that were described by Dr. Lux. It also should be clarified that invasive measurement procedures do not change the study to intentional exposure because such measurements do not result in intentional exposure to the study substance. The document should highlight that "observational" is not equivalent to "no risk" and should emphasize that such studies require ethical evaluation. Bulleted summaries of chapter highlights would improve usability of the document. Clarification of statements regarding scientific validity and examples are needed. Minor language changes were recommended to strengthen the impression of NERL ownership of the recommendations provided in the document. Although epidemiological studies are not included in the scope of this document, such studies can inform ethical and scientific issues relevant to observational research.

Specifically regarding Section 2, the broad opinion of the Board is that ethics is not tangential to science and science is not tangential to ethics. This concept needs to be more clearly articulated. Sample size and selection are important recurring issues related to scientific validity. The document should underscore the purpose, value and scope of observational studies by providing examples of studies to help justify the use of human participants and indicate why alternative models or approaches do not provide the necessary scientific data. The use of "innovative design" in Section 2.1 should be changed. Inclusion of educational materials in a study should be considered as part of the risk-benefit analysis. Clarification of anticipated and unanticipated events, adverse or otherwise, is needed.

The document should provide further examples of non-obvious conflicts of interest. A discussion of adverse events in Section 7.8 could be included in Section 2 to relate such events to the science. For example, if a study is intended to identify a toxic level of a substance as an adverse event, the science must inform this level. Unforeseen uses of data are more appropriately discussed in the section related to informed consent. If the data gathered in these studies become private health information, for example, if an exposed participant must be treated at a hospital, the data may fall under HIPAA rules. A paragraph could be added indicating that NERL has yet to determine an approach to such a situation. Information also is needed describing prevention of data falsification.

Dr. Kim reiterated that the entire document is silent regarding survey sampling relevant to exposure assessment. The sample size determination method included in the document is irrelevant and information exists that describes how to properly determine sample size; this information should be referenced. Dr. Cupitt explained that not all the studies covered by this document are large, randomized, population-based studies. Some of the studies are very small or involve methods evaluation, in which purposeful sampling may be more appropriate. He agreed that NERL would expand the section and clarify that the document applies to many different types of studies with different sampling designs. Dr. Fisher agreed that sampling issues are important for all types of studies. If a study is not representative, well controlled, adequately powered, or lacks a plan for subject attrition, it is not scientifically valid.

Dr. Sharp opened discussion of Section 3, which pertained to vulnerable populations. He stated that this section was comprehensive, well balanced, and particularly clear regarding involvement of children in exposure research. The document takes a moderate position with regard to over- or under-inclusion of vulnerable populations. The document emphasizes the importance of justifying participation of vulnerable populations and that it is preferable to exclude members of such groups if feasible. He suggested that the document provide a clearer distinction between federal regulatory definitions of "vulnerable" and lay impressions of this term. Ecologically disadvantaged populations and people of advanced age are regarded as vulnerable for informed consent purposes, but federal regulations do not necessarily consider these groups to be vulnerable. With respect to observational studies, workplace-based studies are highly important. The unique vulnerabilities of participants in such studies should be described and emphasized. This section is not as well documented as other sections and thus misses an opportunity to familiarize the reader with relevant and useful information.

Dr. Jerry Menikoff agreed with Dr. Sharp's assessment. He added that the section should expand on the duties researchers have toward vulnerable subjects, such as how to appropriately disclose risks to children. He added that the section could expand on the definition of vulnerable groups, because some such definitions may be context specific. Including a clear discussion of reasons for inclusion of a vulnerable population should be considered. Excluding a vulnerable population *a priori* may be a disservice because they may have a greatly increased risk of exposure; thus, excluding such groups would limit the generalizability of the data.

Dr. Ryan noted that observational studies offer less risk compared to intervention studies. With the emphasis this document places on observational studies, it is less compelling to protect vulnerable subjects and more compelling to include them because this will increase understanding of risk in children, pregnant women, and other vulnerable groups. He agreed that *a priori* exclusion of vulnerable populations is a disservice and may ultimately place these groups at higher risk. Dr. Lebowitz noted that vulnerable populations must sometimes be over-sampled because they are more highly exposed to the substance in question. This becomes an environmental justice issue; unless studies purposefully sample these populations, EPA cannot protect the public to the best of its abilities or understand the high end of exposure and risk. He added that vulnerable populations also could be defined by socioeconomic status, diagnosable illness, or demographic information. Dr. Chadwick pointed out the under federal regulations vulnerability refers to the ability to give informed, rational, and voluntary consent to research. Dr. Fisher clarified that, for example, people with asthma would be considered

vulnerable but not necessarily "research vulnerable" in a study of how asthma is affected by everyday exposures; such people should not be excluded, because participation does not render them more vulnerable. If someone is vulnerable because of participation in the research, for example, they have impaired consent capacity; the question is whether the research could mitigate their vulnerability by fitting consent procedures to their cognitive capacities. More sophistication is needed in this section. The burden of defining vulnerable participants does not rest on the participants.

Dr. Sharp noted that the document addresses risk-benefit analyses. He agreed that these studies generally pose minimal risk, but collateral observations may increase risk. For example, if illegal activity is observed during the course of the study, extreme risk to participants may occur. As another example, participants in a study of hog farming practices were harassed by those with a commercial interest in these practices. Dr. Fisher agreed that assessment of risk must include social risk as well as physical or biological risk. Federal regulations state that if procedures to protect confidentiality are sufficient, the study poses minimal risk to participants. Dr. Chadwick noted that the document clearly defined "vulnerable" according to regulations. Regulations do not discuss vulnerability as related to risk, but as related to respect for persons and informed consent processes. Dr. Fish added that regulatory language emphasizes vulnerability to coercion or undue influence.

Dr. Sharp continued with discussion of Section 4 which addresses privacy concerns related to conduct of research in settings such as private homes or schools. The document competently distinguishes between privacy threats posed by a researcher witnessing activities of the participant versus activities of someone who did not consent to participate. This section provides a sound discussion of incidental findings and requirements to report illegal activities. The section also calls for sufficient advance notification of visits to inform those who are not participating in the research but may be at the research location. The document also discusses possible problems associated with observation of monitoring equipment by neighbors or other non-participants.

The document is not sensitive to issues concerning protection of innocents, i.e., how to handle abusive behavior observed by research staff. Research staff should be trained to recognize child or elder abuse both to provide opportunities for intervention and to prevent false accusations. Additional material is needed to address steps to take when situations associated with imminent harm are observed, such as if a researcher observes that a child is in danger of falling into a swimming pool. Attention should be drawn to potential risks to research staff and the staff also should be alerted to potential moral burdens if the staff witnesses troubling or morally objectionable behavior.

Dr. Fish agreed with Dr. Sharp's assessment. She noted that the section describing certificates of confidentiality (page 42) should note that such certificates do not diminish the need to protect personally identifiable information and does not relieve the requirements for reporting illegal behaviors. Dr. Lois Lehman-Mckeeman agreed with Dr. Fish and added that the document should clarify when certificates of confidentiality are needed. The document states that certificates should be used for "sensitive matters," but it does not define sensitive matters.

Dr. Fisher noted that regulations exist that clearly define populations needing certificates of confidentiality and suggested that such regulations be quoted in this section of the document.

Dr. Janice Chambers questioned whether other members of the household would constitute third parties who would need to be informed of the research. Dr. Fortmann explained that this depends on the study. For example, landlords constitute third parties; some researchers exclude renters because informing landlords can be difficult. This issue is complex because if researchers identify a situation in which a renter is exposed to unacceptably high levels of a substance and the landlord is informed, the landlord could create trouble for the renter. Dr. Fortmann explained that it was beyond the scope of the document to provide solutions to all possible situations. The document emphasizes the need for community feedback to help cope with such situations. Dr. Fisher asked Dr. Fortmann to define "participant," because federal regulations are aimed at participants; informing a third party thus may be discretionary. This might require prior identification of a "unit" of participant, such as a family. Dr. Fortmann responded that part of the document review process includes determining whether a third party should be considered to be a subject. Dr. Fisher noted that exposure to risk not associated with the experimental method may or may not define third parties as subjects. Dr. Sharp commented that third parties should still be protected against harm; for example, third parties must be protected against contracting a disease secondary to something like a vaccine administered to another person. They must be informed about this potential risk. Dr. Fisher noted that it is difficult to determine what to require of a researcher beyond regulations, but falling under the standard of "good citizenship." Dr. Philpott described three levels of information requirements: legally required, ethically obligated, and morally praiseworthy. Dr. Fish added that because this is a "best practices" document, discussion of behaviors beyond those required by regulations is appropriate. Dr. Fisher added that researchers also will have to consider reporting laws regarding child and elder abuse that differ among states, with respect to what is legally required. Dr. Cupitt responded that the document does not outline requirements of each state, but includes this topic in the section on data and safety monitoring. He agreed that the document was intended to describe best practices and how to implement them.

Section 5 of the SEAOES document focused on creating appropriate relationships. Dr. Chadwick stated that he would provide some suggestions for wording changes to Dr. Cupitt after the meeting. Dr. Chadwick remarked that the section adequately and clearly discussed researcher responsibilities and provided solid guidance for creating relationships. Weaknesses included a number of discussions and descriptions that were correct, but applicable to other types of research; the document should focus on examples related to observational research. Section 5.1.1 is particularly problematic in this regard; he advised Dr. Cupitt to add more relevant examples to this section. Dr. Chadwick also suggested reconsidering global statements that provide no explanation of importance and instead focusing on statements that are informative. Sections 5.2 and 5.3 provided sound summaries and identification of key points without repeating information verbatim. This section could provide more definitive statements concerning how observational exposure research should be performed. Dr. Chadwick advised reviewing community-based participatory research literature and information from the good clinical practices literature, both of which are relevant to observational studies.

Dr. Chambers agreed that the document was well written and commented on the usefulness of the text boxes. She stated that the scientific aspect of this section seemed light. She also suggested adding discussion of how to describe a study without influencing participant behavior, perhaps by instructing researchers to consider additional comprehension testing. Dr. Chambers commented on the lack of explanation of the statement regarding encouraging retention by providing feedback. She also noted that individual IRBs have different practices and asked how their requirements would be made consistent across the final study and whether Dr. Lux's office had influence over this matter.

Dr. Lebowitz agreed that Section 5 accurately and clearly described the technical relationship between investigators and participants within the context of a community, including respect for social and cultural practices. The section related to compensation was relevant and well written. Section 5.4 provided useful information and Section 5.5 provided a sound discussion of IRB guidelines. Text Box 5-3, which described selecting sub-populations from an ethical viewpoint, also was useful, as was Text Box 5.6, which described retention. Dr. Lebowitz asked the authors to more clearly define "strong scientific relationship," specify Office of Management and Budget guidelines on remuneration, and define whether participant grievance procedures should include EPA or the IRB that approved the study. Weaknesses of this section include the discussion on recruitment in Section 5.5. This section does not address the scientific reasons for stratified sub-populations, or use of overexposed or vulnerable groups. Environmental equity and justice also should be addressed. Section 5.5 also requires material on statistics, generalizability, and sampling methods. In response to the charge questions, Section 5 identifies major issues and areas for ethical consideration. Additional sources of information should be considered for inclusion, such as the 1991 NAS report, EPA and National Institutes of Health (NIH) documents on environmental justice and equity, and documents on building community relationships. Dr. Johnson suggested that recruitment comments could be moved to Section 2. Dr. Cupitt acknowledged that this was possible, but noted that recruitment issues also are relevant to community relationships.

Dr. Fisher summarized discussions of Sections 3, 4, and 5. With respect to vulnerable populations, the Board recommended differentiating between the federal definition of "vulnerable" versus other definitions and highlighting that the federal definition focuses on the ability to defend one's own interests. Justification of the use of vulnerable populations must be emphasized, as should over- or under-exclusion of such groups. Examples of the benefits of including vulnerable groups in observational exposure research could be given. A distinction also should be made between populations that are vulnerable versus research-vulnerable. The section discussing workplace-based studies should be expanded to include citations and better documentation. A section may be needed to describe staff training issues related to privacy and confidentiality, and for training to recognize abuse to avoid over- and under-identification of abuse. Procedures for determining appropriate actions to take in situations of immediate harm should be added and also a protocol for protection of research staff. Confidentiality should be clearly defined and both researchers and participants informed of appropriate confidentiality measures. Third party consent issues should be discussed in terms of legally required, ethically obligated, and morally praiseworthy actions. The difference between inducements and compensation should be clarified; literature exists that defines these terms. The authors also should consider determining when a protocol add-on (such as educational tools) becomes a form

of inducement or a research benefit. More examples appropriate to observational studies should be included. The Board made several suggestions regarding verbiage and clarity of the text. How to describe the study without influencing participant behavior also should be considered.

Regarding the consistency of IRBs, IRBs should provide a baseline of protection. This document can help to increase IRB consistency. The appropriate procedure for addressing participant grievances (through an IRB or other body) should be described. Descriptions of recruitment, over-sampling, and stratified cluster methods could be placed within Section 2. The benefits of longitudinal follow-up also should be addressed.

Dr. Parkin opened discussion of Section 6, which focused on building community and stakeholder relationships. This section identifies important areas and issues to address regarding the ethical aspects of such relationships. A text box describing the major necessary ethical principles and considerations for observational studies should be included in this section. Clarification should be made between moral principles and best practices and also the boundaries of ethics regulations. The distinction between "community" and "stakeholders" should be clarified. For example, stakeholders can speak for a community, but may not be seen by the community as speaking for the community's interests. The legitimacy of the stakeholder may help distinguish between stakeholders and community. Researchers also should identify whether a community has officially conferred upon a spokesperson the ability to speak for their interests.

This section also should discuss how forms of communication should align with community preferences for receiving and conveying information. This is essential for demonstrating respect for community interests. Pilot testing of communications tools should be included. Empirical strategies can be used to ensure the communication forms used by the research will succeed. The section also does not address the fact that relationships are dynamic and may change over the course of the study. A tool that is helpful for monitoring the dynamics of a relationship is an article by Mitchell et al., that describes a stakeholder algorithm used in business settings that also is useful for health matters. Power, urgency, and legitimacy are characteristics that determine the importance of the stakeholder, aspects of the relationship, and with whom researchers will need to work. Researchers should define ways to monitor relationship dynamics and ways to be responsive to these changing dynamics. Dr. Parkin recommended clarifying the verbiage on page 69, lines 6 through 8, regarding the education and capabilities of community representatives; the wording could be considered by some to be insulting or judgmental.

Dr. Buck Louis noted that a statement found throughout the document concerning the idea that bad science is unethical might imply that good science is always ethical; this should be clarified or removed from the document. The science and ethics for observational exposure studies are similar to those for nonexperimental designs and the regulatory description of an observational design is equivalent to a nonexperimental design. Regarding Section 6, the attention to stakeholders is unbalanced with respect to community and other issues, which gives the impression that participation of stakeholders is unimportant. Work addressing evaluation of community advisory boards is available through EPA and the National Institute of Environmental Health Sciences and references to this work should be included. Software is available to measure reading comprehension and grade levels for written materials to ensure

appropriate communication. Dr. Buck Louis cautioned against using only race and ethnicity as examples of cultural differences and recommended including other examples. She also explained that NIH requires data sharing plans, including a timeframe in which participants will receive the data to which they are entitled; such plans are critical for observational exposure studies, particularly with respect to delivering data to participants in a timely manner. Dr. Buck Louis also cautioned against implying that the researcher becomes an advocate for the community; this can raise serious issues regarding moral and ethical conduct.

Dr. Ryan agreed with Drs. Parkin and Buck Louis' assessments. Another problem he noted was that much of the information presented in this section did not have associated scientific references. Examples of community-based research could be used to enhance this section. Section 6.1 provides advice that will be particularly helpful for the neophyte investigator who has just begun to work within a community. A reference to an EPA workshop in Section 6.1.1 and related subsections should be supported with a reference to a publication of proceedings of that workshop. He agreed with Dr. Buck Louis that attention to stakeholders should be expanded. Stakeholder support from local governments and industry is needed to conduct this research.

Dr. Brimijoin stated that he strongly disagreed with Dr. Buck Louis' suggestion that bad science in a study is inherently unethical directly implies that good science is always ethical. He noted that the document tends to under-emphasize the importance of high-quality science. He suggested retaining the phrase in the document, but perhaps stating once that the converse (good science is ethical) is not true. Dr. Buck Louis described an experiment on Sudden Infant Death Syndrome with an observational design that was scientifically valid and reproducible. The investigators argued for the need for parents to place their dead infant back in the crib to minimize recall bias related to sleep position; while this is a valid scientific approach, it is unethical. Dr. Brimijoin noted that the HSRB exists to prevent such situations.

Dr. Fisher summarized that there were underlying concerns for Section 6, particularly that this section does not contain sufficient specific information to be useful. This section also does not clearly articulate the advantages and disadvantages of engaging a community in research, nor does it clearly describe best practices. Investigators should be advocates for the data, not for the community. For example, if an investigator finds pollution that would result in condemning housing, the investigator cannot withhold the data. Investigators should respect and inform the community, but they are not advocates for it. This could lead to conflict between an investigator and a community that does not want the results of the research performed within the community to be disseminated. Procedures for addressing such a situation are not clear. Community groups could be provided with an opportunity to critique the research, or a statement could be included in the disseminated materials indicating community disagreement.

Vulnerable populations within a community are not clearly described. The ethical determination of an investigator's primary responsibility, whether it is to the community or the participant, must be made. A community advisory board is not a substitute for ethical decisions. The composition of community advisory boards is not well defined. Such boards should be representative of the community, but community advisory boards are often staffed by volunteers, which may decrease representativeness. Stakeholders also can include agencies that work with

the community or provide healthcare to the community. Care must be taken not to insult community members who may have helpful knowledge but may lack formal education. Dr. Fisher suggested that NERL address these issues by using existing, published information to provide examples. This section should emphasize the need for a good relationship with the community; good relationships are often built through interactions with stakeholders and community advisory boards.

Dr. Fitzpatrick opened discussion of Section 7, commending the clarity of writing and the use of text boxes. This section focuses on communication and stresses the need for a formal communication plan, which should be considered early in the research process. The definition of stakeholder is unclear; at the beginning of the section, the community is defined as the stakeholder, but this is contradicted elsewhere. This section suggests engaging all stakeholders early and often. It is critical to identify important stakeholders, but care should be taken not to engage too many people with diverse interests. This could lead to conflict that may interfere with the success of the research. References on managing conflict could be useful in this section.

Section 7.3 calls for making announcements early so the community is aware of the next steps in the research process. The researcher should obtain community support before announcing that the research will be performed. This section also calls for using "plain language," but references to Web sites or other publications that explain this should be included. Section 7.5 describes strategies for communicating with subjects, and descriptions of communication materials including a pediatric flyer; the section should clarify that information for children should be presented at a level the children can understand. The section describes using the Internet for communication, but alternative approaches also should be suggested if many members of the community do not have Internet access. The investigator should ensure that the community can access the communication tools. Section 7.6 discusses educating the community about the role of the study; the investigator should consider whether this will cause participants to change their behavior. The effects of education before versus after observation should be balanced. Section 7.7 calls for providing research results to the participants, but the investigators should ensure that the participants understand the relevance and have the resources to understand the data and obtain additional information if they so desire. Participants also should have the option of not learning the results of the research. The community and stakeholders should be informed of publication of research results prior to publication. Information on litigation could be included in the section on grievance procedures and responding to criticism.

Dr. Parkin considered this section to be problematic. She noted the heavy emphasis on one-way communication (i.e., written materials); this is problematic because exposure studies require intimate interactions. Certain aspects of the comprehensive strategic communication plan are not appropriate for community-based exposure studies. The Strategic Risk Communication Plan of Health Canada as referenced in the document is out of date. Dr. Parkin stated that the importance of formative evaluations, which permit evaluation during the research process to ensure that mechanisms being used are appropriate and fit into the participants' culture, was missing from this section. Formative evaluations can help prevent conflict and improve conduct of the study, and also help investigators demonstrate respect for the community.

On page 82, comprehension needs to be correctly identified and empirical testing of communication tools is generally under-emphasized.

Section 7.3 conflicts with the purpose of the document by placing too much focus on how to perform the research and not enough on ethical issues. The tone of the document should be considered with respect to the words, "should" or "must." Dr. Parkin noted that the idea of learning from the participants and the community is missing from the document; adding this would help counteract the over-emphasis on one-way communications. Dr. Parkin described text on page 86 concerning crisis communication and response that perhaps belongs in an appendix. Crisis situations in an observational setting should be rare; perhaps principal investigators could be taught how to recognize an escalating situation. On page 90, language referring to judging perceptions as accurate is problematic because perceptions are not accurate. The difference between lay and researcher perceptions can be acknowledged, but use of the word "accurate" is inaccurate. Dr. Parkin also took issue with the choice of the word "opinion" in this section. Opinions and judgments are different; judgments are considered to be more stable elements of our psyche. Dr. Parkin also suggested that the term "documentation" be changed to "reporting" of the study because some communities may view the term "documentation" negatively. She provided potential sources of information for this section, including the University of Kansas community toolbox Web site (http://ctb.ku.edu/en/), which contains a wide range of communication methods and tools. Further, the RESOLV web site has an excellent booklet by Ms. Gail Bingham focused on best practices for conflict resolution.

Dr. Buck Louis commented that the section provided an opportunity to address issues related to data sharing, and ensuring that the community hears the results before the general public. This could be an opportunity to call for Web-based data management structures that would help improve data availability. Dr. Krishnan noted a passage on page 101 related to challenges to research on chemicals for which there are insufficient data to inform health standards. He stated that it troubles him when people measure chemicals for which the health effects are not known; strong validation is needed for such research. The investigators should address the purpose of collecting data if no standards or evidence of health effects are available and should provide strategies for interpretation of the data in the absence of such background knowledge.

Dr. Fisher summarized that Sections 6 and 7 overlapped significantly. The Board recommended additional empirical guidance and offered specific references. She thanked Drs. Cupitt and Fortmann for presenting this information to the Board. Dr. Lewis thanked Drs. Ryan and Buck Louis for their participation.

EPA Review of Published Clinical Study of Sodium Azide

Introduction

Mr. John Carley (OPP, EPA) provided background information on the published clinical study of sodium azide (Black, M.; Zweifach, B.; Speer, F. [1954]. Comparison of hypotensive action of sodium azide in normotensive and hypertensive patients. *Proc Soc Exptl Biol Med* 85:11-16.). Sodium azide has been used as a laboratory reagent and a raw material for

production of azide-containing compounds. It is also a pharmaceutical intermediate and serves as a preservative in blood, laboratory reagents, and biological fluids. Sodium azide functions as a gas generant in automobile airbags, but propellants containing sodium azide were phased out during the 1990s in favor of more efficient, less expensive, and less toxic alternatives. Sodium azide has been used to treat high blood pressure and as an anti-neoplastic agent. It is currently proposed for pesticidal use as a replacement for the fumigant methyl bromide, which is used in commercial production of ornamental cut flowers and pre-plant application via drip tape irrigation on beds under plastic mulch, and in golf course turf area renovation and sod farms for pre-plant applications to soil with tarping after application.

The study by Black et al. was conducted in the United States in the early 1950s. The authors were affiliated with the New York Medical College and New York University and also received support from the Leukemia Research Foundation. The study explores previous observations of the ability of sodium azide to lower blood pressure in hypertensive patients. The study reports the results of acute and chronic oral dosing of both hypertensive and normotensive subjects and also reports on follow-up testing in rats with induced hypertension; this confirmed human results and showed that humans are the most sensitive species.

Scientific Considerations

Ms. Nancy McCarroll (OPP, EPA) provided the science assessment of the human clinical study of sodium azide. Sodium azide is a simple molecule with a low molecular weight. It is soluble and undetectable in water, which has led to instances of accidental ingestion. Sodium azide is acutely toxic and accidental ingestion by humans leads to a number of symptoms. The effects of accidental ingestion range from headache, dizziness, and restlessness to tachycardia, chest pain, hyperventilation, hypotension, loss of consciousness, and death. It is plausible that these effects all could be mediated by hypotension. Sodium azide also causes hypotension in hypertensive rats at 0.6-0.7 milligrams (mg) per kilogram (mg/kg).

The study by Black et al. examines acute and chronic phases of exposure to sodium azide. The study involved between 30 and 35 patients with documented cases of hypertension occurring in the previous 1 to 10 years; several of the patients had kidney damage. Control participants included 9 normotensive individuals (normal healthy students and laboratory personnel, and cancer patients). The acute phase of this study consisted of oral administration of 0.65-1.3 mg of sodium azide in water (0.01-0.02 mg/kg). The chronic phase consisted of oral administration of 0.65-1.3 mg sodium azide in water at least 3 times per day for periods ranging from 10 days to 2.5 years. Three or more patients received sodium azide via intravenous or sublingual administration. Blood pressure readings were taken prior to administration of the test material. 2-5 minutes after acute administration and 4-12 hours after the last daily dose (for the chronic administration phase). Routine clinical studies of kidney, heart, and liver function were performed on 3 patients and patient complaints were recorded.

Results of the acute phase included a marked decrease in blood pressure 45 to 60 seconds after treatment with 1.3 mg (0.02 mg/kg) of sodium azide in water. No effects were observed in normotensive subjects receiving comparable doses. Results from the chronic phase included a significant drop in blood pressure in 10 subjects (diastolic pressure remained above

100 millimeters (mm) of mercury [Hg]) and blood pressure near normal levels for 15 subjects. No damage to kidneys, heart, liver, bowel, or urinary function was observed in the 3 patients receiving routine clinical studies. Five of the subjects showed only minimal changes in blood pressure. No effects were observed in normotensive control subjects receiving comparable doses of sodium azide for up to 10 days.

Tests of sodium azide in rats included both hypertensive and normotensive rats who received a dose of 0.6-0.7 mg/kg sodium azide by intravenous administration. The blood pressure of the rates was monitored; results showed that doses as low as 0.1 mg (0.6-0.7 mg/kg) induced drops in blood pressure lasting 30 to 45 minutes in hypertensive rats; no effects were observed in normotensive rats at comparable doses. Animal toxicity studies of sodium azide have shown side effects including decreased blood pressure, lethargy, decreased survival with high incidence of brain necrosis and pulmonary congestion, or death. Dogs appear to be more sensitive than rats, developing hind leg weakness at the Lowest Observed Adverse Effect Level of 3 mg/kg per day and central nervous system (CNS) lesions at 10 mg/kg. Hypertensive rats also are more sensitive to sodium azide than normotensive rats.

Limitations to the human phase of the Black et al. study include a lack of demographic information on treated subjects or controls, small sample size, limited clinical testing (none in the acute phase), and use of only three subjects in the chronic phase. For the rat testing, limitations include lack of information on strain, source, age, sex, weight, and the number of test animals, limited information on the test protocol, and data reported only as a narrative summary.

EPA has concluded that the Black et al. study provides evidence that hypertensive humans are more sensitive to the hypotensive effects of sodium azide than hypertensive rats, and more sensitive than the normotensive rats used in toxicology studies. Acute levels of sodium azide that induced normal blood pressure in hypertensive rats (0.6-0.7 mg/kg) were approximately 30 to 35 times higher than the acute dose (0.02 mg/kg) that produced a decrease in human blood pressure within 45 to 60 seconds of administration. These results are consistent with other data that show humans to be approximately 150 times more sensitive than dogs and approximately 250 times more sensitive than rats. This study has been used by other groups including the American Conference of Government Industrial Hygienists, the U.S. Occupational Safety and Health Administration, and the National Institute for Occupational Safety and Health (NIOSH) to set safe levels for sodium azide in the workplace. These threshold levels define permissible limits of exposure incorporating a reasonable margin of safety.

Ethical Considerations

Mr. Carley presented EPA's ethics assessment of the Black et al. study. Documents considered in this assessment include the published report of the study and the EPA Ethics Review of September 27, 2007. This research involved intentional exposure of human subjects to sodium azide in clinical trials as a potential therapy for high blood pressure. The research was conducted over a decade prior to development of the first version of the Declaration of Helsinki, when no explicit standards for ethical conduct of biomedical research prevailed and was not conducted with the intention to submit it to EPA under the pesticide laws, or to any other regulatory authority.

This study was submitted to EPA in September 2005, before the current rules covering third-party human research took effect, so the requirement of 40 Code of Federal Regulations (CFR) §26.1303 to document ethical conduct of the research does not apply. The provisions of the EPA rule that do apply include 40 CFR §26.1602(b)(2) which requires HSRB review because this pre-rule research reports toxic endpoints, 40 CFR §26.1703 which forbids EPA to rely on research involving intentional exposure of pregnant or nursing women or children, and 40 CFR §26.1704 which forbids EPA to rely on pre-rule research if there is clear and convincing evidence that its conduct was fundamentally unethical or significantly deficient relative to standards prevailing when it was conducted. The Black et al. report on the acute and chronic effects of sodium azide on blood pressure in both hypertensive and normotensive subjects is of potential value to EPA to define endpoints for assessing risk to humans from exposure to sodium azide when it is used as a pesticide.

Acute testing was conducted with at least 35 subjects with high blood pressure and chronic testing was conducted with at least 30 subjects with high blood pressure. Nine controls with normal blood pressure included both "normal healthy controls (students, laboratory personnel)" and "patients suffering from diverse types of cancer." The means by which subjects were recruited are not reported, nor are their demographic characteristics. Although neither qualitative risks nor their probability are explicitly discussed, evidence for a general concern for risk reduction includes the use of experimental doses far below the reported lethal range, close monitoring of subject responses, dose reduction for subjects in the chronic phase who developed sensitivity to sodium azide while participating in the test, and side experiments comparing different dosing regimens to establish the minimum effective dose. This research demonstrated that sodium azide lowered the blood pressure of hypertensive subjects. Societal benefits arising from this research include insights into a potentially effective treatment for hypertension, improved understanding of thresholds for side effects of sodium azide, and evidence that humans are more sensitive than animals to the hypotensive effects of sodium azide. Because complete information is not available, it is difficult to determine whether these benefits were foreseeable at the time the research was conducted, or sufficient to justify the unspecified risks to individual subjects.

Regarding independent ethics oversight, the report does not provide information on ethics oversight nor does it identify standards of ethical conduct. Subject confidentiality was not compromised in the published report. The report does not describe what subjects may have been told about the research or whether they participated voluntarily. To discount the likelihood of a

placebo effect, the authors report that sodium azide "was administered without informing the patient of either the nature of the drug or the change to be expected." Because subjects participating in the chronic phase of testing self-administered sodium azide 3 times a day for extended periods, it is difficult to imagine they did so involuntarily.

40 CFR §26.1703 forbids EPA to rely on research involving intentional exposure of pregnant or nursing women or children. Neither the age nor the sex of the subjects was reported. There is no evidence to suggest that any subjects were pregnant, nursing, or less than 18 years of age. It is EPA's policy interpretation that 40 CFR §26.1703 does not prohibit reliance on a study when evidence concerning subject age and reproductive status is absent and unobtainable.

40 CFR §26.1704 forbids EPA to rely on pre-rule research if there is "clear and convincing evidence" that its conduct was fundamentally unethical or significantly deficient relative to standards prevailing when it was conducted. Although there are major gaps in documentation of ethical conduct of the research, there is no clear and convincing evidence that the research was fundamentally unethical. Because a clearly applicable standard of ethical conduct is absent, the research cannot be found significantly deficient by prevailing standards. EPA thus concludes that there is no regulatory barrier to the Agency's reliance on this research.

The Agency has concluded that this study contains information sufficient for assessing human risk resulting from potential acute and chronic exposure. The Board is asked to comment on whether the study is sufficiently sound, from a scientific perspective, to be used as the POD to estimate a safe level of acute and chronic exposure to sodium azide. The Board also is asked to address whether there is clear and convincing evidence that the conduct of the study was fundamentally unethical or that the conduct of the study was significantly deficient relative to the ethical standards prevailing at the time the research was conducted.

Clarifying Questions

Dr. Krishnan requested Ms. McCarroll clarify her statement concerning the numbers of people treated for hypertension using sodium azide. Ms. McCarroll explained that there are approximately 50 million people in the United States who have hypertension and approximately half are receiving treatment. The most common treatment for hypertension is diuretics, many of which contain a component of azide. Sodium azide currently is being validated for limited use. Dr. Krishnan asked for clarification of the number of people in the study evaluated for toxicity. Ms. McCarroll explained that only three of the subjects in the chronic phase of the trial received a toxicity evaluation. Mr. Carley added that all participants were monitored for drops in blood pressure, which was also considered by EPA to be a toxicity evaluation.

Dr. Krishnan noted that the dose used in rats in the Black et al. study was similar to that determined by a broader evaluation of sodium azide performed in 1988 and listed in EPA's Integrated Risk Information System (IRIS). EPA's assessment of the Black et al. study determined a No Observed Adverse Effect Level (NOAEL) of 0.06 mg/kg for normotensive humans. Ms. McCarroll clarified that this drops to 0.004 mg/kg for subjects who required dosage adjustment because of increased sensitivity to sodium azide. She added that the IRIS value is based on research in rats and EPA has added a 100-fold uncertainty factor and an

additional 3 factors to account for chronic use of the substance. Dr. Krishnan asked whether it was necessary for EPA to be able to consider this study, given its lack of information on the purity of the sodium azide, unclear reporting of dose level (listed as between 0.65 and 1.3 mg sodium azide in water), unclear reporting of dosing schedule (sodium azide was given 3 to 4 times or 3 to 5 times), and lack of information on participants' body weight, race, or age. Additionally, 2 years of administration does not truly constitute "chronic" use. Ms. McCarroll explained that information from this study would be used together with accidental ingestion data to determine a dose response. She agreed that examination of only 3 participants for clinical effects was a limitation of the study. EPA has limited data on sodium azide and the Black et al. study provides information on doses that are significantly different from those used in animal studies. The rat study also supports dose-response data and was performed using lower doses. Dr. Brimijoin agreed that the study was not strong, but may provide crucial information because it is the only study that found that humans are significantly more sensitive to sodium azide than other species. Mr. Carley agreed that the Black et al. study best demonstrates that humans are the most sensitive species and focuses on different endpoints than other studies. The values from the Black et al. study also are endpoints that are unmodified by uncertainty factors.
Dr. Brimijoin countered that the data itself is uncertain; the study supports that humans are more sensitive to sodium azide, but provides less clarity on the degree to which they are more sensitive. Dr. Fisher stated that because Mr. Carley and Ms. McCarroll believe the study provides useful information for EPA, the Board must make its recommendations based on that assumption.

Dr. Lehman-Mckeeman clarified that based on the effects in the more sensitive hypertensive population and the need to reduce dose in some participants because of increased sensitivity, EPA is recommending that a dose of 0.25 mg be used to assess human sensitivity. Ms. McCarroll confirmed this. Dr. Lehman-Mckeeman stated that the animal data showed that the two primary targets of sodium azide are the cardiovascular system and CNS, but the Black et al. study includes no evidence of CNS effects. Oxygen is a key reactant for sodium azide and both the cardiovascular system and CNS require large amounts of oxygen. Ms. McCarroll explained that this was probably because the dose used by Black et al. was too low. The animal studies demonstrate that a dose of 10 mg/kg per day is needed to observe brain necrosis; hypotension is likely the most sensitive endpoint.

Dr. Sharp questioned whether there was any evidence that the rat experiments were performed prior to or concurrent with the human testing. Ms. McCarroll responded that this was unknown. Dr. Sharp inquired how hypertension was defined in the study, given that this has changed over the years. Ms. McCarroll explained that hypertension is defined in the Black et al. study as having a blood pressure of 140/90 mm Hg, which also is the value used by the NIH.

Dr. Kim noted that the pounding headache reported in the Black et al. study likely is CNS-related. He inquired about the lack of information in the report. There are discrepancies in the way that the data from the chronic and acute phases of the trial are reported and discrepancies between the data reported in the figures and the data reported in the tables. Figure 1 shows data from 35 subjects in the acute phase of the trial and Figure 2 shows data from 30 subjects that also are listed in Table 2; there appears to be a sizeable overlap between datasets. Given this overlap and other gaps in information, Dr. Kim stated that he was concerned about data from subjects that were not reported in both the figures and the tables. He also stated that

this study did not meet the scientific standards existing at the time it was performed. The first reported clinical trial from the Medical Research Council in England in 1948 in the British Medical Journal included the trappings of modern clinical trials; the results of this trial were reported in a manner similar to that used currently.

Mr. Carley explained that EPA wishes to use the data from this study to assess risk associated with sodium azide use in pesticides. To assess risk, EPA requires information on endpoints, uncertainty factors, and behaviors that produce exposure. This data would be used as a POD for determining the risk of sodium azide associated with its proposed uses.

Public Comments

Dr. Judith W. Hauswirth of Keller and Heckman LLP, on behalf of American Pacific Corporation and Mr. Douglas Richards of American Pacific Corporation

Dr. Judith Hauswirth (Keller and Heckman LLP), on behalf of American Pacific Corporation (AMPAC), stated that AMPAC is pursuing registration of a sodium azide formulation (20 percent in water) as a methyl bromide replacement for non-food uses. The formulation will be colored with blue dye, ammonia will be added, and strong buffering agents will be used to prevent volatilization. Although it is intended to replace a currently used fumigant, sodium azide is not itself a fumigant. AMPAC believes that there is no clear and convincing evidence that this study was fundamentally unethical or significantly deficient according to the standards prevailing in 1954, and agrees with EPA that the study is scientifically valid.

The purpose of the Black et al. study was to investigate the effects of sodium azide as a potential antihypertensive in humans. The study found that sodium azide was effective for lowering blood pressure in hypertensive subjects at dosage levels of 0.65 to 1.3 mg per day on an acute basis; these doses had no effect on normotensive subjects. Chronic doses as low as 0.25 mg reduced blood pressure in hypertensive subjects with no adverse effects on kidney, liver, or heart function. The study was terminated when subjects demonstrated increased sensitivity to sodium azide's effects. The study enrolled sufficient numbers of hypertensive subjects, and there is evidence that these subjects had been diagnosed with chronic hypertension. The study does contain deficiencies, such as a failure to consider confounding factors such as smoking. The study was conducted using methods and equipment standard for the time.

Based on this assessment, AMPAC disagrees with EPA's assessment that the Black et al. study contains sufficient data to use to determine a POD. The study does not determine a clear NOAEL for the effects of sodium azide on blood pressure in normotensive individuals. Because of these weaknesses, AMPAC believes that this study should not be used to determine a POD. AMPAC considers the animal data to be more suitable for determining a POD. Additionally, another study exists (Trout et al.) in which exposure levels to sodium azide and effects on humans in the workplaces were observed. Based on NIOSH levels, expected effects such as dizziness, etc., were not observed. Only one person showed signs of hypotension, but there was no documentation of this. The author of the study was surprised that the NIOSH levels had been set so low. The primary effect found by this study was a transient, acute, pounding headache that

disappeared very quickly. The rat study described in Black et al. used intravenous administration of sodium azide, which is irrelevant to the proposed regulated uses of sodium azide.

Dr. Lehman-Mckeeman asked if AMPAC would use data from rats or dogs to develop a POD if the information from Black et al. is not used. Dr. Hauswirth explained that data from dogs would be used since dogs are more sensitive to sodium azide than rats. Dr. Fisher inquired how exposure to sodium azide was likely to occur. Dr. Hauswirth responded that workers could be exposed dermally, there is a low chance of vapor inhalation, and oral exposure would occur only intentionally. Because dermal exposure is most likely, a dermal exposure study in rats was proposed.

Mr. Doug Richards (AMPAC) represents the manufacturer of sodium azide. He explained that the workplace study described by Dr. Hauswirth was performed at his plant. The study, which was an observational exposure study performed in 1994, measured dermal and inhalation exposure.

Board Discussion

Scientific Considerations – Sodium Azide Study

Dr. Krishnan opened the science discussion by noting that he had two primary concerns: dose and toxicity evaluations. There is no clear indication of a precise dose. The report indicates that doses between 0.65 and 1.3 mg sodium azide in water were used, subjects received the dose between 3 and 5 times per day, and there is no information on body weight or age. The text indicates that doses were reduced to 0.25 mg when subjects showed sensitivity. EPA is using 0.25 mg to calculate the NOAEL, but this value does not appear in the protocol or the results. Dr. Krishnan stated that he was concerned about the lack of information on a 0.25 mg dose and noted that the actual doses used in the study varied by a factor of 8. Concerning the toxicity evaluation, of the 35 participants in the study, only 3 were evaluated for toxic endpoints. The report does not clarify which methods were used to evaluate liver or kidney toxicity and there is no justification of consideration of these organs as target or critical organs. Pounding headaches were reported, but it is unclear whether this should be considered a real effect or should be discounted for determining a NOAEL. It is unclear how a dose of 0.25 mg would correspond to a NOAEL. It is clear that sodium azide lowers blood pressure, but the report fails to provide sufficient information to establish a NOAEL.

Dr. Lehman-Mckeeman agreed that the dose and toxicity evaluations were critical. The data on sodium azide were gathered differently than usually occurs, with data on humans collected before data on animals. Dr. Lehman-Mckeeman believed that there was reasonable evidence that humans are more sensitive than animals regarding blood pressure effects, but it is not clear if humans are more sensitive for other effects. Animal data suggests that the cardiovascular system and CNS are the target organs for sodium azide, thus, assessment of liver and kidney probably was irrelevant. Participants in the Black et al. study did present with transient sensations of head pounding; it is unclear whether this was related to the drop in blood pressure, but this would constitute an adverse effect. She expressed concern that the increase in chronic use appeared to be accompanied by an increase in sensitivity. Of the 20 subjects who

required a decreased dose, there is no information concerning the basis on which a need to decrease dose was determined. She concluded that the study is not suitable for determining POD; data from the study using dogs would be more appropriate.

Dr. Fisher summarized that the Board was concerned about the lack of clarity of doses used in the Black et al. study, and by the lack of clarity of toxicity levels and characteristics. There were also questions regarding whether a drop in blood pressure was useful for establishing the NOAEL, the relationship of this data to the animal data, and concern about the organs used to assess toxicity.

Dr. Kim stated that if the Board finds the data itself acceptable, he did not have concerns about EPA's conclusions regarding this study. Dr. Brimijoin commented that he believed the responsible scientific approach is to comment on the data itself, regardless of how EPA will use the data. The study lacks important information and also was performed as a medical study; there may have been a bias to under-report toxicity and the study was not designed to assess NOAEL. Dr. Brimijoin added that he accepted that this study shows that humans are more sensitive than rats. The data also show that human blood pressure measurement is a much more sensitive indicator than any published measurements from rat or dog studies. Besides the rat data presented at this meeting, other animal data does not indicate whether humans are the more sensitive species. Dr. Brimijoin remarked that he was uncomfortable with the statement that the data from this study are suitable for establishing a probable NOAEL and that the data do not support the conclusion that humans are not sensitive to sodium azide and thus sodium azide can be used in the environment. However, he did consider the data to be sufficient to confirm or anchor existing calculations concerning a POD based on extrapolation from human data. The data are not strong enough to claim that the existing POD should be lowered to account for increased human sensitivity.

Dr. Fisher questioned whether the Board could recommend that these data show that humans have an increased sensitivity to sodium azide. She asked Board members to comment on the value of using the data to estimate POD. Dr. Sharp responded that the Board should defer to EPA's opinion that the study contains additional usable data. Dr. Fisher clarified that two points needed to be addressed: whether the data are sound enough to be used to estimate POD and whether the data are sound enough for EPA to require further assessment. Dr. Brimijoin explained that the data are not sound enough for determining POD; however, the data are sufficiently sound from a scientific perspective to support continued use of extrapolation from animal data indicating the NOAEL, and confirming that the proper POD for humans would be a dose approximately 100-fold lower than that used in rats. Dr. Fisher summarized that the Board had reached a consensus that the data in this study are not sufficiently scientifically sound to be used as a POD to estimate a safe level of acute and chronic exposure to sodium azide.

Dr. Lebowitz suggested adding that the data from the study are informative when combined with information on sodium azide that EPA has from other sources, and EPA can use the data to extrapolate from the animal data. The study is informative because it shows that humans are more sensitive to sodium azide, but not sufficiently scientifically sound to determine POD. Mr. Carley inquired whether the data could be used in conjunction with new animal data

to inform uncertainty factors. Dr. Lebowitz remarked he could not answer that question because the Board has not seen this new data.

Dr. Krishnan noted that the study identifies 0.004 as the NOAEL which appears to be the same as the current reference dose. Normally, an uncertainty factor would be applied to the NOAEL, which would result in a 100-fold lower acceptable dose compared to the current dose. Humans appear to be more sensitive to sodium azide than animals, but this comparison should be based on body surface area, not just on body weight. Based on differences in body surface area and weight, it is not clear that humans are 10 times more sensitive to sodium azide than rats. Dr. Krishnan argued against the conclusion that the data in the Black et al. study was sufficiently scientifically sound to confirm the relevance of animal data. Dr. Brimijoin asked whether Dr. Krishnan would consider the information to be sufficiently sound to be informative if EPA seeks support for existing values and added that the data should not be used to drive exposure limits in either direction.

Dr. Fisher inquired whether the Board could limit the value of the study to permit its use only to confirm animal data and not to establish limits. Dr. Lebowitz explained that this data would allow EPA greater consistency in using existing numbers based on results in animal studies. Dr. Lehman-Mckeeman noted that in general, the data suggest species-specific differences in sensitivity; however, there are problems with dose normalization that may erode this difference. The comparisons also are poor. Dogs often are used for cardiovascular assessments, but the Board does not have information on the effects of sodium azide on blood pressure in dogs and thus cannot make direct comparisons. Dr. Lehman-Mckeeman suspects that the species sensitivity is accurate, but the data do not strongly support this. Additional data points also exist that show no effect on blood pressure in humans, although the Board has not seen this data; it does, however, undermine the confidence in reproducibility of this study. Based on the lack of dose normalization and the possibility of contradictory data, Dr. Lehman-Mckeeman stated that the data fail to support the claim of increased sensitivity in humans. Dr. Fisher summarized that the Board concluded that the data was insufficiently scientifically sound to support use of this data to estimate POD or to extrapolate from animal data.

Ms. McCarroll clarified that the workplace study contained information from an individual who had three separate readings of low blood pressure. In dispute was the comment by the registrant that the individual was hypertensive. This individual had normal blood pressure one week after the reported drop in blood pressure; thus, it is unlikely that this individual was hypertensive. Dr. Fisher commended Ms. McCarroll for her concern for public safety, and underscored that the Board had to limit its recommendation to the quality of the data presented in the article.

Ethical Considerations – Sodium Azide Study

Dr. Sharp opened discussion of the ethics of the study by stating that the study was not fundamentally unethical according to prevailing standards. The study had an acceptable risk-benefit balance. The statement that sodium azide "was administered without informing the patient of either the nature of the drug or the change to be expected" could be interpreted as

blinding rather than deliberate deception. Dr. Chadwick agreed with Dr. Sharp. The protocol called for self-administration of sodium azide 3 times per day for 2 years, which appears to indicate consent; however, in 1954 a cancer patient likely would follow the instructions of his doctor regardless of consent, so this rather rigorous dosing protocol does not necessarily support consent. Despite this, the consent process probably was consistent with 1954 guidelines. Dr. Fish agreed with Drs. Chadwick and Sharp and declined to add to the discussion.

Follow-up From Previous Day's Discussion

Mr. Jordan had no comments on discussions from the October 24, 2007 session.

Science Issues in Mosquito Repellent Efficacy Field Research

The three consultants for this session of the meeting were introduced. Dr. Raj Gupta is the Director of Research Plans and Programs at the Walter Reed Army Medical Center, U.S. Army Medical Research and Material Command. Dr. Steve Schofield works in the Department of National Defence for the Canadian Forces Health Services Group Communicable Disease Control Program. Dr. Daniel Strickman is a National Program Leader with the U.S. Department of Agriculture (USDA) Agricultural Research Service.

Mr. Jordan presented an overview of science issues in mosquito repellent field research. The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) requires EPA to register mosquito repellent products as pesticides. EPA permits repellent products to carry label claims describing the duration of protection from mosquitoes and requires data from field studies to support such label claims. EPA guidelines describe generally how to perform field efficacy studies. Testing at two ecologically distinct sites is required for testing mosquito repellents. The studies should measure "protection time," which is defined as the interval from application of the test material to the occurrence of an event indicating efficacy failure. Permissible label claims must be consistent with the results of field testing to determine protection time. Until the rise in incidence of West Nile Virus (WNV) infections, EPA permitted protection time to be measured as percent repellency, which was calculated by determining the number of bites to treated areas versus untreated areas. Currently, EPA does not accept this measure because of WNV concerns. EPA also has considered moving to "landings" rather than bites to evaluate efficacy failure.

Because these are guideline-responsive studies that meet the regulatory definitions of "intentional exposure" and "research with human subjects," the studies require HSRB review. The Board has reviewed several protocols and completed mosquito repellent efficacy field studies. To aid in its review of such studies, the Board has requested expert consultation on several science issues relevant to the evaluation of new and completed protocols.

The Board and EPA developed discussion questions (Attachment D) for the three consultants which focused on scientific issues related to repellent testing. The discussion questions, categorized in 3 issues, included Board requests for scientific basis/rationale on:

(1) Factors Affecting Repellent Efficacy
(2) Designing for length-based sampling

(3) Complete Protection Time (CPT) in repellent testing vs. failure of efficacy defined as the mean time from treatment to a series of several landings or bites

Dr. Fisher reminded Board members to keep discussion focused on general issues, not specific studies and instructed Board members to reference only protocols presented in the past and not protocols to be evaluated in the future. The goal of these discussions is not to create guidelines but for the Board to be better informed for assessing the appropriate methods, sites, subject selections, and sample size for repellent protocols.

Issue #1

Mr. Jordan presented data summarizing the variability in landing events based on two studies performed by Carroll-Loye Biological Research, Inc. These protocols reported results for 10 subjects at each of two test sites, testing five repellents. All subjects had confirmed landings for each repellent, leading to a total of 20 reported confirmed landings for each repellent. There was considerable variability in the number of unconfirmed landings (between 7 and 14 unconfirmed landings across the 5 repellents). An unconfirmed landing occurs when a mosquito lands on the subject, but no subsequent landing occurs within the time required (30 minutes) to confirm the initial landing. Twenty confirmed landings are expected because once a confirmed landing occurs, the study has ended. The actual number of confirmed landings is greater than 20, because once efficacy fails, many mosquitoes may land simultaneously; within the time period required for the first confirming landing, there may be more than 3 mosquitoes on the subject.

Factors which may affect the variability of initial and confirmed landings include biotic factors such as characteristics of the mosquito population (genus and species distribution, level of ambient mosquito pressure) or abiotic factors, which are related to characteristics of the test site such as season, time of day/brightness, or the microclimate (including temperature, humidity, and wind speed and direction). Other factors that may affect landings include characteristics of the test subjects (such as differences in mosquito attractiveness; use of alcohol, tobacco, or scented products; or behavior). Characteristics of the test methods used that may affect variability include the pattern and duration of exposure, area of skin treated, method used to determine the amount of test material applied, and number of concurrent treatments per subject.

Dr. Fisher asked whether FIFRA requires a confirmed bite to occur within 30 minutes of an initial bite. Mr. Carley responded that FIFRA does not specify this. The data requirements are for regulatory use and do not specify how testing must be conducted; the existing guidelines are advisory, not mandatory. The guidelines refer to different methods and mention time to first confirmed bite; landings are not referenced in the guidelines as indications of efficacy failure, but OPP has been examining this issue. Dr. Fisher inquired whether a confirmed bite is required to establish efficacy failure. Mr. Carley explained that “confirmed bite” is defined in the guidelines as the time to the first pair of bites that occur within 30 minutes of each other. EPA recommends testing to first confirmed bite, but interprets the 30 minute interval loosely; a confirming bite occurring within 31 to 35 minutes is acceptable.

Dr. Gupta presented information on factors affecting mosquito landing or biting activity in a field environment. A repellent is defined as a chemical that causes the insect to make oriented movement away from its source. DEET, Icaridin, and KBR3023 are examples of vapor repellents, which repels the insect before it lands or bites. Permethrin is an example of a contact repellents which permit the insect to land but the insect does not bite and quickly flies away.

Variable factors that affect first or second landing or bite include characteristics of the subjects' skin, temperature, age, hair on the skin surface, and the density of the mosquito population at the test site. Usually, mosquitoes will bite within 5 to 15 minutes after the subject enters the area; after that, the mosquitoes have acclimated to the subject's presence and bite much less frequently. Temperature plays a major role in landing or biting activity; an increase in skin temperature is associated with a decrease in repellency. Skin color or type does not have a major effect on landing or biting, and hair on the skin surface has a small effect. The density of the insect population has a major effect on landing or biting activity.

Factors affecting landing or biting activity also include characteristics of the mosquito population and the test sites. There is significant disagreement among researchers concerning the most appropriate mosquito population to use for testing. Density of the population can affect landing or biting activity. The age of the mosquito population also plays a role, with mosquitoes between 5 to 15 days of age being the most avid biters. Susceptibility of the test subjects to mosquito bites also can affect landing and biting, although most people are susceptible to bites. Selection of test sites critically affects landing and biting. Weather, particularly temperature, can significantly affect biting behavior; repellency decreases by 8 minutes for every 1 degree Celsius ($^{\circ}$C) increase in ambient temperature. Human skin temperature (30-32°C) is considered to be constant. Wind can significantly affect the efficacy of vapor repellents because the wind will quickly remove the vapors; increased wind speed is associated with decreased repellency. Humidity interferes with evaporation and repellency. Light does not appear to have a significant impact because different mosquito populations exist that are active either during the day or at night. The local fauna or flora can impact repellency, especially if the local fauna are the mosquitoes' preferred hosts.

Test subject attraction for mosquitoes is variable. Skin chemistry may have an impact, but the delivery mechanism used to apply the repellent to the skin has a larger effect. Skin temperature is constant and thus has no impact. Skin permeability affects repellency, but it is dependent on the formulation of the repellent.

The effects of test methods are controversial. Sampling methods may vary; for example, continuous sampling requires volunteers to remain in the field and the number of bites is reported, whereas time sampling involves having the volunteers in the fields for fixed periods of time, during which bites are recorded. The time sampling method results in less reduction of the mosquito population at the test site. The skin area exposed also can affect repellency, although the impact of this factor can be reduced by having both treated and untreated surfaces on the same volunteer. Researchers cannot predict the occurrence of either initial or confirming events; the occurrence of a first bite is not informative for the majority of the mosquito population's response.

Dr. Johnson inquired whether "control" in these studies referred to complete lack of repellent or a standard repellent. Dr. Gupta explained that the control could be a person with no repellent on their skin or with a delivery mechanism on their skin without repellent. Dr. Fish questioned whether it was preferable for the same subject to have both control and treated areas. Dr. Gupta responded that a control subject or skin area should be present at the time repellents are tested to ensure that the mosquitoes are biting. Such a control would refer to a different subject. The people serving as controls should be randomized among subjects. Dr. Lebowitz asked about the information available on mosquito behavior garnered from field versus laboratory studies and whether laboratory studies had been performed to address any of these variables. Dr. Gupta replied that his presentation focused on the results from approximately 25 years of field studies performed on 5 different continents employing sample sizes of up to 150 subjects.

Dr. Chambers asked Dr. Gupta to clarify his comments concerning skin permeability. Dr. Gupta explained that the absorption of repellents into the skin ranges from 9 to 50 percent of the active ingredient, and different formulations control absorption through use of different delivery mechanisms. Some formulations use microencapsulation of the active ingredient in polymers that break down and release the repellent upon contact with moisture in the air. Permeability thus is formulation dependent, not skin type dependent. Dr. Chambers inquired how the ability of mosquitoes to acclimate to the presence of volunteers affects extended time period studies. Dr. Gupta responded that there are no accepted theories on this in the literature. Based on multiple studies examining mosquito behavior, he speculated that the mosquito's sensory mechanism is affected by contact with repellent vapors, which compels the mosquito to leave the area. After that occurs, any biting event occurs by chance. Dr. Chambers asked Dr. Gupta to describe chemoreception in mosquitoes. Dr. Gupta explained that mosquitoes are attracted to the heat emanating from the skin surface. Repellents have a limited range of efficacy above the skin surface and the degree of repellency depends on the concentration of the active ingredients.

Dr. Fisher asked Dr. Gupta to explain his statement that biting occurs only by chance after the mosquito has acclimated to the presence of subjects. Dr. Gupta explained that landing is highly variable and not reproducible. Biting is a more discrete event and easier to observe. Mosquitoes usually feed for 60 to 90 seconds and thus biting mosquitoes are easier to collect. If a bite occurs after 15 minutes, this indicates that the repellent has failed and it is unnecessary to expose the subject further. Dr. Schofield explained the mosquitoes locate hosts by a non-directional search. If a mosquito happens to fly close to a subject, the mosquito can detect cues such as carbon dioxide, which provides the mosquito with a direction. This could occur within the first few minutes of a study if a subject happens to come into contact with a nearby mosquito. After this occurs, equilibrium of random contact with mosquitoes is reached. Dr. Fisher inquired whether this means that the time to landing is extended whether or not the subject has applied repellent. Dr. Schofield responded that this was incorrect. A higher recruitment of mosquitoes to the subject occurs initially, but the equilibrium of recruitment changes because attraction occurs from random directions. Dr. Gupta added that the initial detection of movement as subjects enter the test area also tends to attract mosquitoes.

Dr. Brimijoin questioned whether a quantitative or mathematical curve exists that would describe the likelihood of receiving a bite after applying repellent, given the ability to take measurements in a field environment with a stable amount of hungry mosquitoes. He asked the consultants to describe the time course of biting as the repellent evaporated or was absorbed and whether it would exponentially approach equilibrium or if such a graph would indicate a stepwise approach to or sudden failure. Dr. Gupta responded that a repellent curve would indicate higher protection at the beginning of testing and then a decrease over time as the repellency diminished. Dr. Strickman explained that the curve would depend on the test site and species examined. For example, in a continuous collection study occurring throughout the night, if the repellent is applied before biting begins, a rise in biting activity occurs and peaks at approximately 9 PM (or 3 hours after sunset), and then another peak occurs just before dawn. Temperature affects biting; if it is colder than expected, the mosquitoes will bite earlier in the evening. The phase of the moon also influences biting activity. An average periodicity that varies rapidly can be found, but will be different on different nights. Most repellents show either rapid failure within a short time period or diminished repellency (to 90 percent) within 2 to 3 hours and further loss of protection (80 percent then 50 percent) subsequently.

Dr. Chadwick noted that the Board needs to consider the practical implications of its recommendations for parameters that would render a study scientifically sound. For example, because movement in a field test apparently can impact mosquito attraction, requiring subjects to move may be desirable because it more accurately mirrors the typical use of the repellent. Dr. Gupta explained that the research he is most familiar with was performed to test whether a repellent would protect soldiers. It is logistically difficult to collect mosquitoes from a moving subject, so studies were performed using paired volunteers; treated soldiers would perform their regular activities and then be observed for 5 to 15 minutes (the maximum number of bites would occur within 15 minutes). Once a control subject received 25 bites, they left the area, but treated subjects remained in the area for the entire 15 minutes. The number of bites received by treated versus control soldiers was compared. Biting activity is different at different times of the day, so the studies were designed to have subjects in the field at peak activity times using staggered start times to capture biting activity within a 24-hour cycle. The sample sizes used in these studies depended on the number of treatments tested. Usually the studies called for one control subject, one subject treated with a standard repellent, and 5 subjects treated with the repellent being tested. Dr. Fitzpatrick questioned whether treated subjects and control subjects shared factors that could affect biting likelihood. Dr. Gupta replied that pre-selected controls would bias the study and should be selected at random. Differences in experience collecting mosquitoes would bias results; a more experienced subject might collect more landing or biting mosquitoes.

Dr. Fisher asked Board members to consider whether investigators submitting protocols for Board approval should be asked to provide information and a rationale to address the factors listed by Dr. Gupta that affect biting (such as temperature, test site, etc.).

Dr. Johnson inquired if the goal of most repellent efficacy studies was to determine whether a repellent was significantly different from another repellent or to determine efficacy independently. Dr. Gupta explained that most studies examined efficacy to establish if the repellent provided 90 percent of the protection of a different repellent. Dr. Chambers questioned whether military researchers use complete protection time (CPT) to quantify efficacy. Dr. Gupta

responded that they do not use CPT because of its high degree of variability and lack of reproducibility. As an alternative to CPT, percent protection at a given time interval is calculated. For example, the number of bites occurring on a control subject versus a treated subject is determined at 0, 2 and 4 hours and relative protection is determined based on the number of bites. Dr. Chambers questioned how conclusions concerning protection can be drawn given that field conditions vary from day to day. Dr. Gupta replied that the minimum number of days needed to account for this is determined as part of the experimental design. Studies have ranged from 3 to 12 days in duration. The same repellent would be tested on different days. Dr. Kim noted that if an investigator is concerned about the impact of a given variable (such as test site characteristics or time of day), this variable will be included as part of the design. These studies have many confounders because of changes in site conditions and observations taking place at different times, and the data thus is uninterpretable.

Dr. Fish requested Dr. Gupta provide the Board with information on how sample size was formally determined for these studies, including assumptions, confounders, and the impact of individual variability. Dr. Gupta explained that this had been addressed in a prior publication. Sample size selection is based on a repeated measure design randomized across treatment arms over 5 days. The desired endpoint is 25 bites and the statistician uses this value plus the number of treatments to determine the number of volunteers needed. Dr. Fisher questioned whether the Board could be provided with the formulas used by the statistician to determine sample size. The Board could consider recommending the use of these formulas to investigators submitting repellent efficacy protocols to EPA. Dr. Kim noted that these were likely standard formulas, but dependent on the endpoints and predicted variability. Effect size also is needed and power calculations cannot be performed without this variable. Dr. Fisher explained that the goal of this discussion was to provide a reference for investigators concerning matters such as outcome measure selection and power analyses.

Dr. Fitzpatrick inquired whether too many subjects at a site could dilute the number of bites received. Dr. Gupta explained that subjects are usually separated by distances sufficient (approximately 10 feet) to ensure that repellent vapors do not interfere with other test subjects. Dr. Schofield added that the impact of a larger sample size on biting was unknown. The number of people present at the site could affect the numbers of mosquitoes entering the vicinity. The presence or absence of subjects treated with repellents also may affect biting of control subjects. Dr. Gupta reiterated that bites were used because data based on landings was highly variable. Dr. Chambers questioned whether the power calculations used for determining sample size in these experiments were irrelevant to discussions of CPT because of different endpoints. Dr. Gupta was unable to answer this question.

Dr. Fisher requested the Board review the categories impacting biting activity and discuss whether this information should be included in repellent efficacy protocols that the Board reviews. The categories included a description and rationale for activity level of the subjects; the type of mosquito population (i.e., population density species); human differences; test site descriptions (i.e., weather, temperature, flora/fauna); the rationale for choosing the sites; rationale for the test method and analysis including outcome measures with respect to sample size; and distance between or density of subjects. Random assignment of experienced versus naïve subjects to treatment and control groups to avoid bias also was recommended.

Dr. Chambers noted that the controls for these experiments are different because these studies use relative protection time rather than the CPT used in the protocols the Board normally reviews; such protocols use controls only to monitor biting pressure. Dr. Lebowitz reminded the Board that they are not setting policy, but instead recommending information that protocols should include to help the Board evaluate the protocols. The design should describe how investigators will handle different variables, how randomization affects the sources of variability, calculation of sample size based on variables and confounders, the number of control and treatment subjects, and the duration of the study (number of days). There are also ethical aspects to each of these variables. Dr. Fisher inquired whether "replication" should refer to testing at two different sites or repeating the experiment on different days or at different times.
Dr. Lebowitz interjected that the Board must be careful when defining "replication." Performing the same study on another day using different subjects is not necessarily replication because of inter-individual variability. Performing the test on multiple days also is not replication nor is using the same subjects at different sites. The duration of an experiment will be determined by design and variables that can be controlled. Dr. Chambers explained that testing at two sites is performed to determine efficacy in the presence of different types of mosquitoes and speaks more to generalizability of results to different kinds of mosquitoes. She questioned whether EPA would use results from a specific site to determine label language if the experiment was performed at multiple sites. Mr. Jordan explained that EPA has no guidance for this; different labelers use different approaches, but usually use the mean protection time of the two sites.

Issue #2

Issue #2 focused on the methodological rationale for the two different "length biased" sampling designs, one that exposes subjects to potential mosquito landings for 1 minute of every 15 minutes and another that exposes subjects to potential mosquito landings for 5 minutes of every 30 minutes. The consultants were asked to consider which design was more widely used in the field and why, and to assess whether the potential effects of variation in the pattern of intermittent exposure on the results of efficacy testing can be isolated from the effects of other variables. If the effects can be isolated, the consultants were asked to discuss whether the direction or magnitude of the effects could be predicted and determine how these influences might be analyzed and accounted for in collecting, reporting and analyzing repellent efficacy data.

Dr. Schofield presented information related to the validity of intermittent sampling to determine First Confirmed Bite (FCB). The two intermittent sampling designs presented in discussion questions under Issue #2 are not standard designs. Relative protection (RP)/intermittent exposure, RP/continuous exposure, FCB/continuous exposure, and survivorship analysis are considered to be standard designs. Test guidelines for a number of different agencies permit intermittent exposure sampling, but different agencies have different guidelines.

Intermittent exposure provides logistical advantages, mimics approaches used in the laboratory, minimizes exposure, and maximizes protection time estimates. Decreased exposure reduces biting pressure and decreases the likelihood of a bite (first or confirming). It was

recognized as early as 1940 that a decreased protection period was proportional to increased biting pressure. Varying the amount of exposure affects biting pressure.

Neither of these length-biased sampling designs is widely used in peer-reviewed and published field studies. The potential effects of variation in the pattern of intermittent exposure on the results of efficacy testing cannot be isolated, predicted, or accounted for because sound information on the impact of intermittent exposure on FCB estimation is not available.

Dr. Lebowitz noted that standard approaches, such as FCB with continuous exposure, have been developed based on different sets of recommendations. The exposure time periods in the two length-biased sampling designs vary slightly and differing opinions exist concerning the time needed to collect sufficient numbers of bites to assess efficacy. Dr. Strickman stated that the time between first and second bites is variable. Dr. Lebowitz speculated that although these exposure regimes are not standard, continued modeling by Drs. Schofield and Strickman likely would result in a series of models, each of which would generally show that decreases in continuous exposure increase the likelihood of overestimating CPT.

The number of variables that may affect the observations, the type of designs that are needed to accurately perform these studies and account for variability, and ways to analyze the results constitute critical information for the Board's evaluation of protocols. However, there is little information on the true impact of variables on efficacy. Dr. Lebowitz stated that more research is needed to define design issues, biases, and other factors; however, designs exist that include randomization and appropriate power calculations that would allow more appropriate conclusions to be drawn. Determining how to adjust for exposure times is an outstanding issue.

Dr. Fisher questioned why EPA called for use of intermittent exposure given that continuous exposure is a standard design in academic research. Mr. Carley clarified that EPA did not choose this approach. Protocols with different exposure methods were proposed when EPA began intensive review of prior exposure research. EPA guidelines do not require or specify intermittent exposure. Dr. Fisher remarked that consistency is important for EPA to compare currently submitted studies with previously submitted studies. Mr. Carley responded that previous studies used both continuous and intermittent exposures, but he did not know how many studies used each approach. The Board has evaluated protocols from only two different investigators, and protocols tend to vary based on the investigator. There is no clear rationale for using different exposure methods.

Dr. Kim remarked that Dr. Schofield's presentation suggested that the sponsor may choose a certain sampling method to artificially increase protection time. Mr. Carley agreed that EPA should consider standardizing exposure time given the many other variables affecting repellent efficacy. Dr. Lebowitz also agreed that standardizing exposure would help minimize variation. Dr. Fisher stated that in the absence of a requirement, a rationale for the use of intermittent versus continuous exposure, the duration and frequency of exposure, and the advantages and disadvantages of both approaches would be useful for Board evaluation of protocols. Dr. Lebowitz added that the Board also should consider its own lack of knowledge. Until the Board is better informed, it will be difficult to understand how an investigator determines their approach. Dr. Fisher suggested that the protocols should provide references to

the academic literature that would enhance the Board's understanding of the design rationale. She clarified that the Board was not stating a preference for continuous exposure, but rather requesting a rationale for the choice of intermittent or continuous exposure. Mr. Carley countered that if each investigator performs a literature review and uses the review to design the study protocol, it will be more difficult for EPA to have consistent data across products. EPA is considering significant changes in guidelines to prevent this. Dr. Schofield agreed that, from a regulatory perspective, guidelines are needed. His research uses a different endpoint—protection of soldiers—than the studies required by EPA. Because the goals of the experiments are different, it is logical that the experiments would be performed differently. Dr. Lebowitz remarked that EPA would benefit from reviewing its own guidelines, military research literature, and other gray literature. Dr. Chambers cautioned that the Board should not expect an extensive literature review to accompany all protocols. Instead, EPA should develop a sense of best practices, which give the best consistency, and revise its guidelines accordingly, keeping in mind that field studies vary greatly.

Dr. Brimijoin described a similar situation in which testing for cholinesterase inhibition by a number of different laboratories using a simple method resulted in a great deal of variation both in how the method was performed and in the results. In response, EPA convened a number of Scientific Advisory Panels (SAP) to develop best practices. The SAPs developed a consensus for how the assay should be performed and had that method validated; this was highly challenging. This approach could be helpful for establishing consistency to repellent efficacy protocols.

Dr. Schofield explained that the relationship between protection time and DEET concentration did not initially appear to be robust. At a given concentration, there was a great deal of "scatter" around the protection time, but the overall analysis showed a powerful relationship. The general pattern of protection time tends to be clear.

Issue #3

Issue #3 dealt with the precision of CPT estimates. Dr. Matt Kramer, a USDA statistician, has suggested that the precision of CPT estimates in repellent testing could be significantly increased by defining failure of efficacy as the mean time from treatment to a series of several [e.g., five] landings or bites. The consultants were asked to determine whether this approach would markedly increase the precision of CPT estimates without requiring additional subjects and, if so, whether the increased precision would justify the incremental risk to the subjects resulting from their exposure to mosquitoes. The consultants also were asked to consider the practicalities involved in testing long-lasting repellents to the point of five landings.

Mr. Jordan explained that EPA is evaluating its approach to the regulation of repellents, with respect to what to test for, how to perform the studies, how to analyze the data, and how to communicate the results to consumers. The regulatory endpoints for efficacy used by EPA are different than those used in military research. EPA requires a degree of certainty to inform consumers, but this must be balanced with the costs of performing the necessary studies. Earlier in 2007, EPA invited a number of experts in the field of repellent efficacy evaluation to discuss methodological issues. The Board and the three consultants received the information and

presentations discussed at this meeting. Dr. Kramer proposed defining efficacy failure as the mean time needed for a series of landings or bites to occur across a subject population. He contends that this could provide a more precise protection time estimate without significantly increasing the number of subjects needed for the studies. The subjects would be exposed to more landings and/or bites, but this may nonetheless be an ethically acceptable approach. There are issues concerning whether this approach is feasible for long-lasting repellents.

Dr. Strickman presented information related to the issue of using multiple rather than single landings for determining CPT. The military has successfully analyzed protection times to establish that a repellant lasts at least 8 hours. Studies costing $1 million have been designed to evaluate efficacy and have been successful; however, these studies are not designed to compare efficacy across repellents in different studies. The purpose of a study must be decided before methods can be defined. Important information concerning vector response to a suite of repellents has been obtained from these studies, and Dr. Strickman cautioned that different types of studies likely will be needed to test efficacy against insects other than mosquitoes.

Graphing the proportion of mosquitoes landing against time shows that the avidity of a population has a normal distribution. Mosquitoes landing either early or late in the defined time interval are rare; most land at a median time. A Poisson distribution also shows this. The Log Dose Probit Precision curve illustrates that the most precise estimate of protection is obtained in the middle of the curve and errors in the estimate increase toward the edges of the curve.

CPT is inherently imprecise because it is based on the actions of a single mosquito. Because CPT is defined as time to first bite, it likely captures the behavior of a mosquito at the edges of the distribution; such mosquitoes are likely to be aberrant in their biting behaviors. CPT is believed by the Agency to be the information the consumer wants; however, most people apply repellent after receiving 2 or 3 bites, not after the first bite. The military determines 95 percent protection, because this value can be determined from the part of the curve that offers greater precision. Determining 90 percent effectiveness will offer better comparison across products. Precision and confidence are enhanced by using multiple landings, and there is no additional risk to subjects because landings are used rather than bites.

Dr. Strickman explained that, in his opinion, the multitude of variables in the field make specific comparisons between studies almost hopeless. Laboratory tests could be standardized for a strain of mosquito/tick, and could eliminate most variability from subjects. The precise number of actual hours of protection is always a rough estimate because of other factors (use pattern, dosage, weather, etc.). EPA labeling standards can inform the consumer accurately about the relative duration of a product through the use of standardized laboratory tests. EPA uses data from efficacy studies to derive relative labeling information, which is different from performance claims for specific conditions. Public health entities may be more interested in real duration of protection.

Dr. Lehman-Mckeeman inquired how the precision of the protection time estimate could be increased. Field studies appear to be unable to provide sufficient precision because of their variability. She asked whether increasing from 1 to 5 bites to indicate failure would increase precision given the inherent flaws and variability in field testing. Dr. Schofield commented that

it is possible that using multiple bites would increase the precision of the arithmetic mean time. Using 90 percent protection also may increase precision, but may not be useful statistically. This may speak to the need for laboratory tests. He explained that a study using 5 bites as failure of efficacy would show a time period in which no bites occurred, followed by the occurrence of bites. Graphing cumulative bites over time would give a slope that could provide perspective on efficacy and would be a useful piece of comparative information. The time within the threshold of the curve could provide the most important information. Dr. Schofield stated that arguments advocating the use of laboratory studies as opposed to field studies to compare efficacy across products is more appropriate are compelling.

Dr. Kim explained typical statistical inferences used in experiments. A reference point, such as a measurement of time of application, to efficacy is developed, and certain parameters such as time to failure, are estimated. After this is determined, a statistical model is introduced and mean or median plus confidence intervals are determined, depending on the distribution and censoring of data. Based on Dr. Kramer's comments, it is difficult to determine what is being inferred. The time from application to failure is a specific quantity and a statistical inference can be made. The net effect of using multiple landings provides more measurements, but does not necessarily increase precision of these measurements with respect to protection time. Precision is important, but adding subsequent events to determine protection time may push the mean to the far end of the curve. Dr. Strickman noted that the appeal of using 5 landings was based on a study performed in Paraguay in an area with a high density of mosquitoes. A 75 percent formulation of DEET was insufficient to repel early biting mosquitoes (i.e., those found at the far end of the curve). Repellents can appear to fail at high mosquito density, but this represents the behavior of rare individuals.

Dr. Chambers questioned if EPA regulations required field testing. Mr. Jordan explained that the guidelines are not binding. EPA regulations require data and the guidelines suggest how to generate the data to meet the requirement. EPA expects that most of the data will be generated using field tests. Dr. Chambers remarked that Dr. Gupta has presented information suggesting that the effect of mosquito behavior and environmental conditions on repellent efficacy cannot be predicted. Dr. Strickland also has provided compelling reasons for preferring laboratory-based tests. Laboratory-based tests therefore might provide better data for use on labels.

Dr. Fish inquired how labels are generated and what the information on the labels means. In her understanding, if a label indicates that a product is effective for 4 hours, this value was determined from an average CPT developed using field studies. The label may not be intended to inform the public that CPT is precisely 4 hours, but is useful when the consumer is comparing products to buy. If this is true, Dr. Fish stated that the information presented at this meeting appears to decrease the reliability of the CPT on the labels, given the issues with variability. She asked why labeling did not refer to short-, medium-, or long-term protection time; consumers may believe that 4 hours is a precise value. She also expressed concern that the labels may prompt consumers to re-apply the product after less than 4 hours if mosquitoes begin to bite. Mr. Carley agreed that mean CPT is generally developed using data from various studies that are incorporated into the label claims. Labeling serves two purposes; it provides an index that permits product-to-product comparison and can be used for advertising or marketing claims. The

label also includes directions concerning application (i.e., not more than X times per day, avoid contact with eyes) in addition to CPT. EPA is considering use of short-, medium-, and long-term protection in addition to or in place of a precise number of hours.

Mr. Jordan explained that EPA has evaluated repellents since its inception but has not updated its approach. He informed Board members that new information, along with Board suggestions, is being considered. EPA will not recommend switching from field to laboratory testing at this point, but is considering this option. EPA also is not ready to switch from hours of protection to relative protection, but is considering this as well. Decisions also need to be made concerning the need for testing on multiple days, at multiple sites, and if field testing provides information that cannot be obtained from laboratory testing. EPA must consider consumer expectations, how to communicate information to consumers, what degree of uncertainty will be tolerated, the effects of changes on cost, how to transition to a different approach, and historical issues. Ideally, this consideration would be done empirically. EPA is considering grouping products by formulation, percent of active ingredient, or the carriers that may affect dermal absorption.

Dr. Fisher suggested that EPA consider the implications of the use of continuous versus intermittent exposure and the multiple versus single landing approach, which has many implications for product evaluation. She added that given the information presented at this meeting on variability the Board might wish to identify the type of information protocols should include to help justify a particular approach such as different means of exposure, and different ways of measuring efficacy failure.

Public Comments

Dr. Thomas Osimitz and Dr. M. Keith Kennedy on behalf of Science Strategies, LLC and the DEET Task Force

Dr. Thomas Osimitz (Science Strategies, LLC) stated that the DEET Task Force is working to develop a database of DEET and repellent efficacy. The task force will perform a literature and data search on repellent efficacy, using published data, unpublished data, government reports, and industry-sponsored studies. This program will consider the relationship between DEET concentration and protection time (predictive model). Assuming a simple relationship is found, the program will assess the degree of variation (and/or uncertainty) around a predicted protection time, given a certain DEET concentration. The program also will examine whether the protection time versus DEET concentration obtained from laboratory data can be used to predict similar relationships using data obtained from the field (at least for the most common insect species).

The desired outcome of this work is to establish a generic/monograph approach to efficacy for DEET-based repellents, obviate or greatly reduce the need for conducting additional efficacy studies using humans (laboratory and field) for both new products and re-registrations, allow label claims to be determined according to DEET concentration and protection times in the monograph, set standards for levels of protection, save significant time and resources, and reduce human testing.

At the current time, a comprehensive literature search on repellency has resulted in retrieval and review of more than 800 abstracts; 49 articles also have been obtained and reviewed. Collection of industry data has included both submitted and non-submitted studies; 524 studies have been collected and are being reviewed. Overall, the task force has reviewed 48 field studies and 373 laboratory studies.

Preliminary data review of laboratory studies has found that the arm-in-cage testing methodology is remarkably similar across many different test laboratories, although differences in test cage size and the number of mosquitoes used has increased over the last 10 years. Testing on additional mosquito genera (*Culex*, *Anopheles*) is now common practice but the species used are highly variable. Test subject attractiveness appears to be a large source of experimental variability (error). The relevance of laboratory testing to effectiveness in real-world situations is still not clear; however, DEET efficacy appears surprisingly robust over a range of concentrations despite variability of test methods, test subjects, and laboratory-reared insects.

Preliminary data review of field testing studies has found that there is significant disparity in the field test methodology employed by various test laboratories. Key discrepancies include differences in description/calculation of the results (CPT versus percent repellency), lack of a standard procedure/definition for "control," inconsistent reporting of biting rates, lack of a standard practice for the selection and number of test subjects used, and lack of a standard distance for spatial separation of test subjects. These discrepancies in methodology make it difficult to draw comparisons between and among field test studies. The testing of nuisance mosquitoes versus disease vectors also needs clarification (a laboratory versus field issue). Mosquitoes constitute the majority of studies compiled, and only a handful of field studies exist on ticks and biting flies. Several recently published studies were identified that could form the core of a 'best practice' field test method.

The next steps for the Task Force include development of a data dictionary and establishment of criteria for data stratification including study type (laboratory versus field studies, exposure methodology, or location), genera and species testing, and product formulation (lotion, spray, wipes, addition of sunscreen, water-based, solvent-based, regular, or slow release). Data quality also will be evaluated for appropriateness for inclusion in analyses and a statistically rigorous meta-analysis will be conducted.

Dr. Chambers asked Dr. Osimitz to elaborate on his statement that DEET shows consistent protection times. Dr. Osimitz explained that there was a strong relationship between DEET concentration and protection time.

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

Dr. Carroll commented that when he entered the field of repellent science, a strong body of work did not exist. Currently, there is potential for gaining much information about this field. He stated that he wished to address issues related to sponsor motivation and field testing conditions.

Regarding relative protection, a SAP meeting held 5 years ago found that continuous testing was stronger scientifically and statistically than intermittent testing. Studies before the new era of EPA regulatory requirements used continuous exposure and calculated relative protection; however, the impression from EPA was that such protocols are not acceptable because of the increased risk to test subjects; thus, intermittent exposure was used. This resulted in gathering data from 10 subjects every 15 minutes, with obvious limitations for statistics.

Dr. Carroll commented that in his experience, basing methodology on maximizing CPT has never been a point of discussion with a sponsor with respect to study design. The goal of most sponsors was to determine if a product did not work. Intermittent exposure requires an ambient biting pressure of one bite on the control arm within the designated exposure interval; this is a higher biting pressure than required for continuous exposure experiments. Intermittent exposure does not, therefore, maximize CPT. Regarding lack of appropriate controls in field testing, determination of appropriate controls will be dependent on effect size.

Board Discussion

Dr. Chambers acknowledged that the field is in a state of transition and that EPA should develop new guidance. She stated that the Board must work with current information and place less emphasis on future directions because EPA is considering changes based on expert advice.

Dr. Parkin inquired whether the purpose of the studies was clear in the regulations. Mr. Jordan explained that EPA has regulations that are focused on data requirements. These requirements specify that EPA requires appropriate data for registration of a product, but do not specify which data are needed to support claims of repellent efficacy. The purpose of EPA labeling is to help consumers understand the efficacy of the products and to give a sense of relative protection across different products. The guidelines are not regulatory requirements, but instead are suggestions; however, they are generally given considerable weight and sponsors adhere closely to them. The guidelines indicate an interest in protection time from the point of application to efficacy failure. The guidelines currently specify bites as indicative of efficacy failure, but EPA is moving toward use of landings. This information is in the public domain. Dr. Parkin noted that, without empirical research on what consumers need and how they understand the information, whether the data helps consumers understand efficacy cannot be determined. Although this is a different domain of research than that sponsored or undertaken by EPA, such research could be considered. Mr. Jordan remarked that EPA would consider this.

Dr. Sharp commented that it may be helpful for Board evaluation if a section of the protocols the Board reviews focused on the rationale for using field studies versus laboratory-based testing. This will affect interpretation of both scientific and ethical challenges, particularly if the same data can be obtained in a safer (i.e., laboratory) environment. Dr. Lebowitz stated that the day's discussions provided a framework for the Board to use to understand and judge completed studies in terms of method, results, and other factors. This information will be critical to the Board's ability to provide advice to EPA considering appropriate designs and protection of the public with respect to repellent efficacy testing. Dr. Chambers questioned whether EPA currently requires field testing. Mr. Jordan responded

that the guidelines provide guidance, but not requirements. Companies almost always perform field testing and EPA expects to see field testing. Dr. Chambers inquired whether landings always result in bites. Dr. Strickman replied that most mosquitoes land and do not bite. At high densities, mosquitoes may land randomly and may not bite nor have any intention of biting. Determining intent to bite is difficult. Probing can be observed, which is more indicative of biting, but probing presents as much risk as a bite, because viruses can be transmitted with the first probe.

Dr. Fisher concluded that based on the presentations and board discussion information that would be useful to the Board includes rationales for sample size, outcome measures, number of treatment groups and controls, why a field study is preferable, why a specific environment was selected, how different environments differ, and how controls for environmental shifts in temperature or time of day are determined. The Board understands that the need for smaller sample sizes and the accompanying lack of power must be balanced with subject protection, but it is also important to understand which variables can be controlled. The expertise of control and treated subjects with respect to detecting mosquito landings must be balanced and the activity of subjects also should be controlled.

EPA Review of Completed Efficacy Studies by Carroll-Loye Biological Research: SCI-001 and WPC-001

Introduction

Mr. Carley provided background on the completed protocols SCI-001 and WPC-001. Protocol SCI-001 was reviewed by the Board in January 2007, and executed by Dr. Carroll in July 2007. The field testing results were reported separately for each of three test formulations, which included two registered products and a third product that was neither registered nor the subject of an application for registration. The study reports as submitted—taken together with the supplemental materials provided on September 24, 2007 in response to EPA's request—meet the standard of completeness defined in 40 CFR §26.1303. Because this research was initiated after April 6, 2006, it must be reviewed by the Board.

Protocol WPC-001 was reviewed by the Board in April 2007, and executed by Dr. Carroll in July 2007. This protocol tested a single conditionally-registered repellent product containing Oil of Lemon Eucalyptus (OLE) for efficacy against mosquitoes in the field. The study report as submitted, along with supplemental materials provided on September 20, 2007 in response to EPA's request, meets the standard of completeness defined in 40 CFR §26.1303. Because the study was initiated after April 6, 2006, this completed study must be reviewed by the Board.

SCI-001 and WPC-001 were both conducted by Carroll-Loye Biological Research. Both protocols used essentially equivalent recruiting strategies and drew from the same pool of volunteer subjects; many subjects participated in both studies. Both protocols had similar objectives and followed essentially the same experimental design. The protocols were executed concurrently at the same sites; untreated controls were shared, as was some data. There were some key differences between the two protocols. SCI-001 tested three DEET repellents; each

was compared to a military standard and reported separately. WPC-001 tested only the repellent containing OLE. SCI-001 was not amended to describe the process for recruiting untreated control subjects, but WPC-001 was amended. SCI-001 used one consent form for both treated and untreated subjects; WPC-001 used separate forms.

The SCI-001 protocol was revised on December 14, 2006, and reviewed by EPA on December 20, 2006. The protocol and consent documents were further revised on December 29, 2006 and approved by the Independent Investigational Review Board, Inc. (IIRB) of Plantation, FL on January 2, 2007. The consent document was corrected on January 22, 2007. The protocol was reviewed by the Board on January 24, 2007. The report of the January 2007 HSRB meeting was issued on April 16, 2007.

The WPC-001 protocol and consent documents were drafted on January 16, 2007. The protocol was approved by the IIRB on January 23, 2007, reviewed by EPA on March 13, 2007, and reviewed by the Board on April 18, 2007. The HSRB report of this meeting was issued on June 13, 2007. The protocol and consent documents were amended (separate forms for treated and untreated subjects were created) on June 14, 2007. The amendment and consent documents were approved by the IIRB on June 19, 2007. On July 4, 2007, the consent documents were further revised and these were approved by the IIRB on July 10, 2007. The consent documents for untreated subjects were further revised on July 12, 2007, and the final versions of these documents were approved by the IIRB on July 13, 2007.

The sponsor of SCI-001 asked to add LipoDEET 3434 to the protocol on June 30, 2007, and the protocol was amended to add it on July 2, 2007. Depending on when approval to add this was received and when consent forms were signed with respect to study initiation, addition of LipoDEET 3434 may have adversely impacted the consent process. The study was initiated on July 3, 2007, and dosimetry testing occurred on July 3, 4, and 5, 2007. Field testing took place on July 7, 8, 12, 13, 14, and 15, 2007. WPC-001 was initiated on July 10, 2007. Treated subjects signed consent forms on July 10, 11, and 12, 2007, and controls signed consent forms on July 11 and 16, 2007. Dosimetry testing occurred on July 10 and 11, 2007. Field testing took place on July 12, 13, and 15, 2007. Comparison of the execution schedules of the two protocols showed that the initiation dates were staggered by a week, although limb measurements took place at the same time. Tracking the daily activity of each subject showed that some subjects were not excluded if they had used repellent on a previous day, in violation of the exclusion factor stating that subjects were not to use repellent 24 hours prior to testing. On one day of testing, all 5 materials were tested simultaneously, which may have resulted in subjects failing to maintain the necessary distance between one another because of the large numbers of people in the test area. Addition of LipoDEET 3434 to the protocol and violation of the exclusion factor requiring subjects not to use repellents 24 hours before testing could be significant issues.

Different numbers of subjects were treated with each repellent each day, for a total of 10 subjects for each repellent at each of the two test sites. This raises questions concerning whether partial data can be summed across different days of testing. If subjects are dropped for violating the 24-hour repellent use ban exclusion factor, the number of subject days of testing for each repellent at each of the two sites drops below 10 (range was 4 to 8 subjects). Additionally, if subjects treated with LipoDEET 3434 are dropped, 66 of 100 subject treatment days are lost.

The number of subject days of testing each repellent at each site drops below 10 (range was 4 to 8 subjects). If subjects treated with LipoDEET 3434 or with any repellent 24 hours prior to testing are excluded, the number of subject days of testing drops to between 0 and 3 for each repellent at each site. The largest sample size thus is 3 and this is derived through pooling of data.

In letters dated October 19, 2007, Dr. Carroll responded to EPA's science and ethics reviews of SCI-001 and WPC-001. EPA's concerns about these protocols included the complex entanglement of the execution of both protocols; treatment of subjects on successive days in violation of an exclusion criterion applied to both studies; the unreviewed amendment to SCI-001 that changed the test material (inclusion of LipoDEET 3434), which potentially affects two-thirds of all the data; and pooling of field data from different test days at the same site, which may comprise the design sample size.

Scientific Considerations

Mr. Kevin Sweeney (OPP, EPA) reviewed objectives and study design for the protocols. The objectives of SCI-001 and WPC-001 were to test the mosquito repellent efficacy characteristics of the test materials in the field, support proposed label claims for extended duration of efficacy of three slow-release DEET products, meet a condition of registration for the OLE product, and determine a "typical consumer dose" for each test material.

Each protocol included a dosimetry phase. Each subject's lower legs were measured and skin area was calculated. The dosimetry phase established the "typical consumer dose" of each test material for use in efficacy testing. In SCI-001, each of 10 dosimetry subjects applied each of the 4 test repellents 3 times to each leg. In WPC-001, each of 10 dosimetry subjects applied the OLE pump spray 3 times to each leg. The grand mean of subject means was calculated for each test material, to be used as the standard dose rate for that material in the field. The standard dose rate was converted to an individual dose for field testing by adjusting it to individual subject leg area.

Both protocols also called for aspiration of landing mosquitoes. Before participating in field testing, subjects were trained in the laboratory to aspirate landing mosquitoes before they bite, using laboratory-reared, pathogen-free mosquitoes and hand-held electric aspirators. Subjects in field testing were equipped with aspirators, and worked in teams to watch each other for landing mosquitoes. Untreated subjects were attended by two technicians to assist in aspirating landing mosquitoes.

For the field efficacy phase of the protocols, 10 subjects treated with each formulation and 2 untreated control subjects participated in field trials in each of 2 habitats. Because of the expected long duration of efficacy, subjects were treated with the test repellents before traveling to the test site. Untreated subjects were used to monitor mosquito pressure and treated and untreated subjects were exposed to mosquitoes for 1 minute at a time every 15 minutes until efficacy failure.

The sample size of 10 subjects per treatment at each site, with 2 concurrent untreated controls, was justified in the protocols with rationales considered by the Board in previous reviews of similar Carroll-Loye protocols. Given the Board's comments from previous meetings, EPA is reconsidering this matter in general; however, EPA's current position is that a sample size of 10 treated subjects, which substantially exceeds the size specified in the current draft guidelines, is acceptable for studies of this type.

Both protocols used "Landing with intent to bite" (LIBe) as the endpoint for efficacy failure. Field testing continued for each subject until that subject experienced one LIBe confirmed by another LIBe within the same or either of the next two 1-minute exposure intervals. Duration of efficacy (CPT) was calculated as the time from treatment to FCLIBe. Landing mosquitoes collected by aspiration were subsequently identified and subjected to serological analysis for pathogens. Measured variables for both protocols included subject limb area, weight of test materials delivered to the dosimetry subject's limb (DEET lotions) or to gauze dosimeters (OLE pump spray), mosquito pressure (at least one landing per minute on untreated controls), time of all LIBes, and time to FCLIBe for each subject. The mean to FCLIBe, with standard deviation and 95 percent confidence intervals, was calculated consistent with EPA guidelines. The median time to FCLIBe was calculated using Kaplan-Meier survival analysis.

Testing took place at two field sites. The site in Butte County, CA, is characterized by grassland with scattered shrubs and small trees around a small lake. This site is referred to as "Site 1" in SCI-001 and "Site 2" in WPC-001. The second site is located in Glenn County, CA and is situated in the understory beneath the canopy of a tall native forest. This site is referred to as "Site 2" in SCI-001 and "Site 1" in WPC-001. Wild mosquito populations present at the sites included *Aedes melanimon, A. vexans, A. freeborni,* and *Culex tarsalis*.

WPC-001

Dr. Clara Fuentes (OPP, EPA) provided EPA's science assessment of WPC-001. In response to HSRB recommendations, dosimetry testing was conducted outdoors, data capture forms were modified to allow recording of exact placement of dosimeters, and statistical procedures were revised to incorporate Kaplan-Meier survival analysis. The rationale for sample size was not revised. Premature withdrawal of subjects was addressed in amended §9.1.3.12 "Exclusion Criteria, all subjects" and post-testing disease monitoring of collected mosquitoes was performed as per amended §10.4.7.

WPC-001 used a pump spray formulation. The standard dose was determined to be 0.43 milligrams per square centimeters (mg/cm^2), which gave an active ingredient dose of OLE of 0.13 mg/cm^2. The mean total active ingredient dose was 135 mg, which gave a dose of 1.93 mg/kg for a 70 kilogram (kg) adult. The dermal margin of exposure (MOE) of OLE is greater than 2,000 mg/kg and this experiment was determined to have an MOE of 1,036. Twenty-four confirmed LIBes were reported; this is more than the expected value of 20 confirming LIBes because of multiple mosquitoes landing on a subject. Seven unconfirmed landings were reported; there were 51 total landings.

Several protocol deviations were reported. The subjects did not cover their treated limbs between exposure intervals when a screen-house was available, practice rounds for dosimetry phase were reduced from two to one for most subjects, experienced subjects assisted in treatment of other subjects, treatments were applied before travel to test sites, the prescribed inter-subject distances were not maintained on July 12, 2007, temperature data was recorded inaccurately for the first 3 hours on July 12, 2007, and the dose for subject 13 was miscalculated by 0.01 milliliter. The failure to maintain inter-subject distances was considered to be the most serious deviation. Unreported deviations included a failure to acknowledge concurrent execution of WPC-001 and SCI-001 and violation of exclusion criterion by testing subjects who had used repellent on the previous day. The CPTs determined in this protocol were 4.2 ±0.8 hours for Butte County and 6.1 ±1.5 hours for the Glenn County site. Pooled CPT was 5.2 ±1.5 hours.

Study limitations included deviation from the revised protocol by testing more than one formulation simultaneously, testing of different repellents on the same leg the day before testing OLE, and pooling of data for different days without accounting for additional sources of variability. Further clarification is needed to verify the accuracy of the data generated by this study.

SCI-001

Mr. Sweeney presented EPA's science review of completed protocol SCI-001. This protocol tested the efficacy of four registered slow-release lotions containing DEET: LipoDEET 302 (EPA Reg. No. 82810-1), Coulston's Duranon (EPA Reg. No. 50404-8), Insect Guard II (EPA Reg. No. 54287-8), and 3M Ultrathon (EPA Reg. No. 58007-1), which is the U.S. military standard repellent, as a standard of comparison.

At the request of the sponsor, Insect-Guard II was replaced as a test material by LipoDEET 3434, an unregistered repellent. LipoDEET 3434 was inadequately characterized in the report of its testing, and the substitution was not acknowledged in the reports for the other two test materials. In response to EPA's request, LipoDEET 3434 was described as similar to LipoDEET 302, but containing DEET at the same 34.34 percent concentration as the 3M Ultrathon comparison repellent. The rationale for substitution provided in response to EPA's request stated that using a product with an equivalent DEET concentration provided better comparison to Ultrathon and that Insect-Guard II was no longer being marketed.

The standard dose of LipoDEET 302 was 1.61 mg/cm^2, for an active ingredient dose of 0.48 mg/cm^2. The MOE for LipoDEET 302 was 524. The standard dose of LipoDEET 3434 was 1.55 mg/cm^2, for an active ingredient dose of 0.53 mg/cm^2. The MOE for LipoDEET 3434 was 499. The standard dose of Duranon was 1.51 mg/cm^2, for an active ingredient dose of 0.30 mg/cm^2. The MOE for Duranon was 861. The standard dose of Ultrathon was 1.27 mg/cm^2, for an active ingredient dose of 0.44 mg/cm^2. The MOE for Ultrathon was 594. DEET concentrations for each product were 30 percent for LipoDEET 302, 34.34 percent for LipoDEET 3434, 20 percent for Duranon, and 34.34 percent for Ultrathon.

Recorded unconfirmed landings for LipoDEET 302 and LipoDEET 3434 were 7 each, 14 for Duranon, and 8 for Ultrathon. All repellents had more than 20 confirmed landings. Confirmed landings were 28 for LipoDEET 302, 22 for LipoDEET 3434, 29 for Duranon, and 27 for Ultrathon. Total landings were 55 for LipoDEET 302, 49 for LipoDEET 3434, 63 for Duranon, and 55 for Ultrathon. CPTs for the combined Butte and Glenn county sites were 9.9 ±1.6 hours for LipoDEET 302, 10.5 ±1.6 hours for LipoDEET 3434, 8.83 ±1.6 hours for Duranon, and 10.1 ±2.3 hours for Ultrathon.

A number of study limitations were noted. Although the protocol called for random selection of treated limbs, the method used to choose which leg to treat was not reported; data suggest that subjects who participated on more than one day were treated on the same leg each time. Many subjects were treated with different repellents on consecutive days, or with the same repellent on multiple days. Data for the same repellent from the same field site but at different times on different days were pooled for analysis. Data analysis limitations included inadequately addressing the potential for drop-outs in the analysis plan (although there were no drop-outs—all subjects received a confirmed LIBe), failure to analyze the distribution for normality, failure to assess the potential impacts of "date effect" or "time effect", and analysis of variance (ANOVA) was reported only for SCI-001.3.

Clarifying Questions

Dr. Kim inquired how subjects were randomized. Mr. Carley explained that this was not reported in the study and is considered by EPA to be a limitation. Dr. Johnson asked about the rationale for using LipoDEET 3434. Mr. Carley responded that proceeding with this change without IIRB review was a significant issue and asked the Board to comment on the impact of this substitution on other data in the study if the results from subjects treated with LipoDEET 3434 were dropped. Dr. Kim added that another science issue related to this substitution was the possibility of carryover. Dr. Sharp questioned how LipoDEET 3434 compared to Ultrathon. Mr. Sweeney replied that the DEET concentrations of these two products are the same. The carriers are different, but the carrier used in LipoDEET 3434 is similar to that used in LipoDEET 302. Dr. Philpott asked if there was information about the risks associated with repellents formulated using liposomes; this could affect the justification for substituting LipoDEET 3434. Mr. Sweeney explained that there is acute toxicity data for liposomes, which were not developed for use only with repellents. EPA has not conducted a separate evaluation of liposomes because they are not considered sufficiently toxic to warrant this activity. Mr. Sweeney added that there are other slow-release DEET formulations, but LipoDEET 3434 and LipoDEET 302 are the only to use liposomes. Dr. Chambers inquired if EPA had information on the kinetics of the formulations, particularly regarding dissipation from the skin surface. Mr. Sweeney explained that this information probably was available for Ultrathon, but may not be available for the other three formulations.

Ethical Considerations

Mr. Carley provided EPA's ethics assessments of the two protocols. Documents considered in review of SCI-001 include the EPA protocol review of December 20, 2006, the April 16, 2007 report of the January 2007 HSRB meeting, and Carroll-Loye Biological

Research's response on September 24, 2007 to EPA's request for more information about LipoDEET 3434. Documents considered in the review of WPC-001 include the EPA protocol review of March 13, 2007, the June 13, 2007 report of the April 2007 HSRB meeting, and Carroll-Loye Biological Research's response on September 20, 2007 to EPA's request for information concerning when subjects signed which version(s) of the consent documents.

Reported protocol deviations include the same six deviations reported for both studies, plus an additional deviation for WPC-001. Two of the deviations have potential ethical significance, namely, the use of experienced subjects to assist investigators with applying repellents to other subjects, and failure of subjects to maintain a prescribed distance from one another. The failure to maintain the prescribed distance was misleadingly dismissed "because all subjects were wearing the same repellent;" subjects were not wearing the same repellent. Unreported deviations include beginning subject limb measurements and dosimetry testing for WPC-001 before the reported date of study initiation and before subjects signed WPC-001 consent forms. Subject 29 participated in limb measurement for WPC-001 on July 7, 2007, 4 days before signing the consent form on July 11, 2007. Subject 60 participated in dosimetry testing for WPC-001 on July 10, 2007, 2 days before signing the consent form for WPC-001 on July 12, 2007. In addition, untreated control subjects signed the final version of the WPC-001 consent form after completion of all field testing. In violation of an exclusion factor common to both protocols, 46 percent of treated subject/days involved prior repellent treatment within a day of testing.

In response to EPA's comment that the SCI-001 protocol inadequately described recruiting of "experienced" subjects to serve as untreated controls, changes were made in the version dated December 29, 2006; no further changes were made after the HSRB meeting. EPA asked that the consent form be corrected to delete references to alcohol in the test repellents; the revisions were made acceptable in the December 29, 2006 version of the consent form. EPA also asked that the consent form be revised or split to better inform untreated controls; the consent form was so revised in the December 29, 2006 version.

Dr. Carroll responded to several HSRB recommendations regarding SCI-001. The protocol was amended on July 2, 2007 to incorporate viral assay of field-collected mosquitoes to confirm the absence of known pathogens. The HSRB requested that the protocol be revised to clarify how untreated controls would be recruited, but this was not addressed further after the HSRB meeting. The Board also asked to see evidence of the IIRB member training, accreditation, and so forth; no additional information about the IIRB member qualifications or IIRB accreditation has been provided. The Board also made recommendations similar to those of EPA, i.e., the informed consent document needed to be changed to correct the erroneous statement that the test materials contained alcohol and the consent form needed to be structured so that it did not apply to untreated control subjects; these changes were made in the December 29, 2006 revision. The Board requested that the protocol be changed to read, "up to 48 (10 exposed and 2 controls per arm of the study)" subjects will participate in the protocol; the informed consent form was not changed from "up to about 40" and the actual number of subjects was 37 to 41.

In response to EPA's requests regarding WPC-001, the data collection forms were changed by June 14, 2007 (amendment 7) to refer to subjects only by coded number rather than name. This version also satisfactorily addressed (§9.1.6.2) the lack of description of how "experienced" subjects will be recruited to serve as untreated controls. The amendment dated June 14, 2007 also deleted references to recruiting in Florida. In response to HSRB recommendations regarding WPC-001, the protocol was amended to add viral analysis of collected mosquitoes, references to Florida were deleted, and separate consent documents were provided for untreated subjects in the June 14, 2007 amendments. The investigator was generally responsive to EPA and HSRB suggestions, with minor exceptions. For SCI-001, the description of recruiting of experienced subjects to serve as controls was not revised after the January 2007 HSRB meeting and the HSRB recommendation to change the SCI-001 consent form to estimate up 48 total subjects was not implemented.

Applicable ethical standards for these two protocols include 40 CFR §26.1703, which prohibits intentional exposure of pregnant or nursing women, or of children under 18; 40 CFR §26.1705, which requires evidence of substantial compliance with 40 CFR part 26, subparts A-L; 40 CFR §26.1303, which requires documentation of ethical conduct; and FIFRA §12(a)(2)(P), which requires fully informed, freely voluntary participation. EPA has found that the protocols comply with 40 CFR §26.1303 and 40 CFR §26.1703. Regarding compliance with FIFRA §12(a)(2)(P), conduct of SCI-001 may have fallen short of the requirement of FIFRA §12(a)(2)(P) that human subjects of research be fully informed of the nature and purposes of the test and of any physical and mental health consequences reasonably foreseeable there from by failing to acknowledge the change in test repellents and to adequately describe LipoDEET 3434 in the consent forms. Conduct of WPC-001 may have fallen short of the requirement of FIFRA §12(a)(2)(P) that human subjects "freely volunteer to participate in the test" by failing to obtain legally effective informed consent from all subjects before involving them in the research.

Regarding the requirements of 40 CFR part 26, subpart K, §26.1108(a)(4), calling for each IRB to follow written procedures and ensuring that changes in approved research are not initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects, the procedures of the IIRB were not effective to ensure that amendments to the SCI-001 protocol that changed one of the test repellents and added a viral analysis of collected mosquitoes were not initiated without IRB review and approval. These changes to the approved protocol were not necessary to eliminate apparent immediate hazards to the subjects. Pertinent aspects of Subpart K, §26.1116, namely that no investigator may involve a human being as a subject in research covered by this subpart unless the investigator has obtained the legally effective informed consent of the subject also may have been violated. In WPC-001, Subject 29 is reported to have undergone limb measurement on July 7, 2007, but to have signed a consent document on July 11, 2007. Also in WPC-001, Subject 60 is reported to have participated in dosimetry testing on July 10, 2007, but to have signed a consent document on July 12, 2007. Additionally, untreated control subjects 6, 13, and 14 are reported to have signed the final version of the consent form on July 16, 2007, after completion of all field testing for WPC-001.

Consideration of whether the protocols showed substantial compliance with 40 CFR part 26, subparts A-L found that execution of SCI-001 was in at least technical noncompliance with

the requirement that all changes to approved research be reviewed and approved by the IRB. Execution of WPC-001 also was in at least technical noncompliance with the requirement that no subject be "involved in research" before providing legally effective informed consent. In other respects both studies complied with applicable requirements of 40 CFR part 26.

EPA concerns regarding protocol SCI-001 include implementation of the amendment changing the test material without IRB review or approval, and the investigator's stated understanding that it is within his discretion to determine which amendments to an approved protocol change the risk-benefit profile enough to require "additional ethics review;" implementation of the amendment to add viral assay of collected mosquitoes, also without IRB review or approval; changing the role of the "experienced subjects" to include service as assistants to the investigators, without amendment to the protocol or consent forms, and without IRB review or approval; failure to modify the consent form to accurately inform treated subjects of the materials to which they would be exposed in SCI-001; failure to acknowledge the change of test material in sub-study reports SCI-001.1 and SCI-001.3; compromise of the exclusion factor prohibiting participation by subjects who had used repellents on the previous day; and failure to acknowledge concurrent execution with WPC-001, and the misstatement that "all subjects were wearing the same repellent" on July 12, 2007.

EPA's concerns regarding WPC-001 include reporting the "study initiation date" as 6 days after data collection began; informed consent discrepancies (limb measurement of Subject 29 before consent, possible participation by Subject 60 in the dosimetry phase before consent, signature of final consent by untreated controls after test completion); changing the role of the "experienced subjects" to include service as assistants to the investigators, without amendment to the protocol or consent forms, and without IRB review or approval; compromise of the exclusion factor prohibiting participation by subjects who had used repellents on the previous day; and failure to acknowledge concurrent execution with SCI-001, and the misstatement that "all subjects were wearing the same repellent" on July 12, 2007.

EPA concluded that there were shortcomings in the conduct of these studies—failures to fully report deviations from the protocols, to ensure documented consent was obtained from all subjects before involving them in research, to report all amendments to the IRB, and to fully inform subjects concerning the test repellents. Mr. Carley's judgment was that these shortcomings did not put the subjects at greater risk than they would have faced had the protocols been executed without exceptions, but, taken together with the other deficiencies noted, they may have compromised the studies such that even the low risks to the subjects were no longer justified by the value of the information obtained. The noted shortcomings represent at least "technical noncompliance" with the cited passages of 40 CFR part 26, subpart K. EPA defers to the Board for guidance concerning whether these shortcomings rise to the level of substantial noncompliance with the requirements of 40 CFR part 26, subparts K and L.

The Board was asked to address protocol-specific issues including whether sequential testing of different repellents by the same subject on successive days was likely to affect the results; whether partial results of testing the same repellent in the same habitat on different days can be pooled to comprise the design sample size and whether this was likely to affect the results; if choice of limb or how it is selected matters if only one limb is treated; whether failure

to maintain a minimum inter-subject distance could affect the results; and the implications for other arms of the study if one arm of a study is deemed unacceptable under 40 CFR §26.1705.

The charge questions to the Board asked if SCI-001 was sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy of the formulations tested against mosquitoes. They were asked to consider, in particular, whether participation in field testing by several subjects on the day after they had been treated with a different test repellent was likely to have affected the validity of the results for those subjects on those days. The Board also was asked to consider the effects of changes to the experimental design that resulted in evaluation of repellents using fewer than 10 subjects per treatment per day, followed by pooling of results by site for statistical analysis.

The Board was asked to comment on whether the available information supports a determination that this study was conducted in substantial compliance with subparts K and L of EPA regulations at 40 CFR part 26. The Board was asked to comment specifically on the decision to use a different test formulation in place of one of the test materials described in the protocol reviewed by the IRB, EPA, and the HSRB, and how to assess the ethical conduct of an insect repellency study involving multiple test formulations when there is an ethical deficiency in the conduct of the study with respect to one of the test formulations. If the ethical deficiency warrants not relying on the results of the testing with regard to one test formulation, the Board was asked to describe circumstances (if any) under which the ethical deficiency affects the acceptability of the results from testing the other formulations.

The charge questions for WPC-001 asked the Board to determine whether research conducted under this protocol was sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy of the formulation tested against mosquitoes. The Board was asked to comment specifically on whether participation in field testing by several subjects on the day after they had been treated with a different test repellent was likely to have affected the validity of the results for those subjects on those days. The Board was asked to address whether the available information supports a determination that the research covered by WPC-001 was conducted in substantial compliance with subparts K and L of EPA regulations at 40 CFR part 26. If the conduct of any part of SCI-001 is deemed not to substantially comply with the requirements of subparts K and L, the Board was requested to comment specifically on how to assess the ethical conduct of research performed under WPC-001 given that it was completed at the same times and at the same places as the research covered under protocol SCI-001.

Dr. Menikoff inquired if the IIRB was informed of changes to the test compound. Mr. Carley indicated that he did not have this information. Dr. Menikoff questioned if changes in a test compound were characterized as a protocol deviation because the protocol was amended. Mr. Carley replied that the important point was that the protocol was changed without IRB oversight and the informed consent forms also were not changed to reflect use of a different test compound. Dr. Fish asked whether there was any evidence that these protocol deviations were reported to the IIRB. Mr. Carley explained that the changes had not been reported. Dr. Kim inquired if the informed consent forms indicated that the subjects would test more than one product. Mr. Carley stated that SCI-001 describes the study as a test of different repellents and indicates that test subjects could be treated with any one of these substances. The informed

consent forms for WPC-001 refer only to the single OLE formulation. Neither informed consent form mentions LipoDEET 3434. Dr. Krishnan questioned if the repeated applications were taken into account when calculating the MOE. Mr. Carley responded that this was not necessary since multiple washings took place to ensure a low chance of interference.

Public Comments

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

Dr. Carroll stated that the protocols and conduct of these studies exceeded previous repellent testing protocols in terms of human protection and that the science on which they are based is sound. The studies were conducted concurrently because of movement of the mosquito population and distribution of WNV that occurs over the course of the year. WNV has become more common, which has narrowed the timeframe during which testing can be conducted.

Concerning spacing of test subjects, Dr. Carroll considered statements regarding violation of the spacing protocol to be misleading. Quality assurance personnel were present on July 12, 2007, and engaged Dr. Carroll and the technicians in discussions which resulted in brief periods of decreased monitoring and brief periods in which the subjects failed to maintain the minimum distance from one another. Untreated controls remained in appropriate proximity to both treatment groups.

Regarding the protocol deviations on the reporting forms, the most serious errors were stated to be failure to seek approval for amending the protocols for virus screening and testing LipoDEET 3434. Dr. Carroll stated that he did not realize that all amendments required IRB approval. Dr. Carroll has taken the online Collaborative Institutional Training Initiative course, and this was not mentioned. Other IRBs have informed him that they only need to review changes that affect subject safety; thus Dr. Carroll was under the impression that there was some latitude regarding the need to submit revisions to the IRB. At this point in time, the protocol changes, as well as minor consenting errors, have been reported to the IRB.

Regarding the distribution of treatments across days and sites, testing on multiple days within a site does not decrease the generalizability of the results. The results showed a major difference between treated and untreated subjects. Concerning exclusion of previously treated subjects, treated subjects reached a point of efficacy failure and then washed the treated area two to three times. Dr. Carroll stated that he did not intend to exclude these people when he designed the protocol. Data from both protocols indicate no effect of prior treatment.

Dr. Chambers asked Dr. Carroll about the ability of soap or alcohol to wash repellants off the skin. Dr. Carroll answered that he does not have data on this, but soap and water work well to remove repellents. A slight temporary decrease in avidity is observed in mosquitoes exposed to recently washed skin in cage testing, but this is believed to be due to reduction in skin temperature and other attraction cues; the efficacy of repellents also disappears after washing. Dr. Chambers inquired whether the repellents tested were contact or volatile repellents and whether Dr. Carroll had information concerning the maximum distance attraction cues could travel to attract mosquitoes. Dr. Carroll explained that the tested repellents were volatile

repellents, but that he did not have information regarding the attraction cues. Dr. Krishnan questioned if subjects treated on subsequent days were treated on the same limb. Dr. Carroll confirmed that these subjects were treated on the same limb.

Dr. Philpott inquired if a Material Safety Data Sheet (MSDS) for LipoDEET 3434 was made available to study participants. Dr. Carroll responded that the participants had received this form. Dr. Philpott asked about the number of personnel present during testing, particularly for days in which many study participants were present. Dr. Carroll explained that two study personnel were assigned to each untreated control. One group leader was designated for each study and three personnel provided support and helped ensure proper segregation. Dr. Philpott questioned if the untreated controls who participated in both protocols signed two consent forms. Dr. Carroll replied that they did sign both consent forms.

Dr. Fish questioned if the protocol deviations listed in Appendix 5 were submitted to the IIRB. Dr. Carroll explained that he did not think these deviations had been submitted. Mr. Carley noted that Dr. Carroll reported that the subjects received the MSDS for LipoDEET 3434 and asked if the subjects saw a different MSDS than the form included in the response dated September 24, 2007. Dr. Carroll answered that he did not think that the subjects saw a different form.

Dr. Kim inquired about the methods Dr. Carroll used to randomize subjects. Dr. Carroll answered that subjects' numbers were drawn randomly by a technician and each subject was assigned to a test material. Dr. Kim remarked that for true randomization, given the total of 13 subjects, each number should have been present in triplicate. Dr. Carroll indicated that the goal was to maintain the same number of subjects within a given treatment compared to Ultrathon over a 5-day exposure period. The design was close to a symmetrical design. The number of subjects within a treatment had been decided before initiation of the experiment. Dr. Kim commented that to balance each day equally, balanced randomization was required. Dr. Carroll responded that, given the way he needed to distribute the subjects among tests that were run simultaneously, the same number of subjects could not always be used each day.

Dr. Fitzpatrick asked whether subjects received treatment on one day and then served as untreated controls on the next day. Dr. Carroll answered that this did not occur, although Mr. Carley clarified that this had occurred in one instance. Dr. Fitzpatrick noted that it did not appear that controls were picked at random. Dr. Carroll explained that control subjects had been selected in advance. Dr. Krishnan inquired if the same number of subjects were involved in the protocols at each location. Dr. Carroll responded that there were 10 subjects per treatment per site, although there was some overlap between sites. Dr. Krishnan questioned whether the violation of the exclusion criteria forbidding subject participation if they had used a repellent 24 hours before testing had been reported to the IIRB. Dr. Carroll replied that this had not been reported to the IIRB.

Dr. Lehman-Mckeeman asked at what time of day the studies started, and about the amount of time between treatments given the length of the study day and that the studies were performed on successive days. Dr. Carroll explained that there was approximately 24 hours between treatments. The test day started at 7:00 AM and continued until approximately 7:00 PM.

Dr. Lehman-Mckeeman asked Dr. Carroll to explain the rationale for forbidding subjects to participate if they had used a repellent within a 24-hour period. Dr. Carroll responded that he had included this criterion because he wanted to exclude people who had used an unknown product with little knowledge of how or when it was applied. Dr. Sharp asked Dr. Carroll if the change to the protocol that allowed participation by subjects who had used repellent within a 24-hour period had been reported to the IIRB. Dr. Carroll answered that this change had not been reported. Dr. Lebowitz inquired whether subjects were exposed for one minute at the beginning of each 15-minute interval. Dr. Carroll replied that there were 15 minutes between each exposure.

Board Discussion

Scientific Considerations – SCI-001

Dr. Chambers commented that the Board may be prematurely reviewing these protocols. She stated that given Dr. Carroll's written responses, he may be able to change his analyses and present a more suitable, modified analysis to the Board. With respect to the consecutive days of treatment, deviation from the protocol may or may not have influenced the results; the evidence is insufficient to judge this deviation. This change did result in a more efficient strategy for completing testing within the designated time periods. Other repellent efficacy protocols do not have this exclusion factor, so it likely is not necessary; however, these products are designed to endure and thus there may have been residual effects. Information on duration of efficacy was not provided.

The results indicate that the CPTs for these products were between 9 and 10 hours. Testing began at 7:00 AM and continued for 9 to 10 hours, so efficacy likely had failed by this point. Subjects then washed the treated areas and any residual effects probably were lost. The results from testing subjects on consecutive days probably are valid; however, crucial information is lacking. Use of a specific limb probably did not have an effect. Regarding distance between subjects, if volatilization of the repellents is not extensive, failing to maintain a proper distance probably had no effect; however, information on this is lacking.

One of the Board's consultants during the earlier mosquito repellent discussion commented that testing over several days was more desirable than testing on one day, which means this protocol was more informative than one testing on only a single day. The impact of the deviations on the data is likely to be small because the data are not expected to be highly accurate. Dr. Chambers stated that she was sympathetic to Dr. Carroll's need to consolidate testing because of WNV concerns. She speculated on the degree of flexibility EPA allows in protocols to compensate for environmental changes; it may be reasonable to allow such deviations. Dr. Chambers summarized that testing on consecutive days did not impact the results, choice of limb did not impact the results, and failure to maintain the minimum distance between subjects also did not significantly impact the results.

Dr. Lebowitz commented that the study had strengths including the dosimetry phase and application of the product by trained technicians. Information was presented earlier in the day that stated that differences in temperature, relative humidity, and light were pertinent to mosquito

repellent efficacy studies. The probable similarity of these factors across days and sites was a strength of the study. Dr. Lebowitz commended Dr. Carroll for testing the captured mosquitoes for WNV and Eastern Equine Encephalitis. The exclusion criteria were appropriate. That untreated controls experienced a minimum of one landing per exposure during 448 of the 450 exposure periods indicates an adequate number of mosquito landings and mosquito density at each site. Dr. Lebowitz also commended Dr. Carroll for performing Kaplan-Meier survival analysis. Dr. Lebowitz criticized the testing of insufficient numbers of treated subjects at each day and site. ANOVA was not calculated correctly or powered sufficiently. The effects of repellent application between 150 and 210 minutes before exposure and the effects of travel to the site are not fully known. Dr. Lebowitz confirmed that FCLIBe was equivalent to FCB.

In response to the charge questions, Dr. Lebowitz stated that he had reached some tentative conclusions based on the fact that the protocol was not followed well in terms of randomization, data pooling, or testing on subsequent days. He added that the effects may not be visible because of the small number of subjects participating in the protocols.

Dr. Brimijoin agreed with Dr. Chamber's assessment. He noted that the key question is whether there is potential for any residue left on the limb 24 hours later to influence mosquito response. This likely had no effect, because efficacy of the repellents was lost within approximately 8 hours, frequent washing of the site occurred, and testing did not occur until the next day; pesticide residue probably did not accumulate. ANOVA failed to detect signs of cross reaction because of the differences between the treatments. A more powerful demonstration of independence could be made if controls served as treated subjects on a subsequent day to determine if efficacy duration was different from that of a never-treated control.

Dr. Johnson stated that the data were too "messy" to analyze. The data do, however, indicate a general measure of efficacy. Concerning whether treatment on subsequent days affected efficacy, of 19 data points derived from subjects treated on the previous day, 12 showed an increase in efficacy duration, 7 showed a decrease, and 4 showed the same duration. This effect does not appear large enough to be significant, but the effect may nonetheless be real.

Dr. Kim explained that more observations generally are preferred, but this requires certain assumptions. Excluding the control observations, there were only 33 unique subjects and 80 data points. Distribution of the subjects across dates, sites, and treatments may not have been properly randomized, which limits analysis. To combine sites, statistical independence of observations is required. In these protocols, overlap between sites occurred and the dependency of overlapping subjects was completely ignored; thus, error measurements are incorrect. Fewer than the expected number of subjects completed testing, and testing was conducted over multiple days, which could account for confounding. Because of the overlap of subjects across repellents and test sites, standard analyses are inappropriate. The protocol indicated that subjects would be randomized across 3 test materials and the control repellent (Ultrathon); the appropriate way to analyze such data is to analyze the 4 test materials together and then perform pairwise analyses of subjects treated with the 3 test materials to those treated with Ultrathon.

Analysis of all 80 data points from the treated subjects showed that not a single censoring event was noted, which implies that all subjects experienced a confirmed bite. The results from a

previous, similar protocol by this investigator (EMD-004) indicated a significant amount of censoring. Even given the variability of mosquito biting pressure, site temperature, and site selection, this is troubling. Dr. Chambers commented that "censored data" referred to individuals who remained in the test site until the end of the test period but did not receive a confirmed bite. Mr. Carley explained that because this protocol called for applying the repellent before going to the test site and was planned for a longer day in the field, it is possible that all subjects received a confirmed bite.

Dr. Johnson commented on the Kaplan-Meier analyses performed for this protocol. Assuming different subjects were in each group, variance analysis would take into account testing of more than one repellent by the same subject and would not treat the subjects independently. The investigator concluded that there was no difference in treatment, but ANOVA indicates there was a difference. It is easier statistically to prove difference than similarity; thus a larger sample is needed to prove that two results are the same. Dr. Johnson indicated that he would like to see the confidence intervals between the means to conclude that CPTs are the same. Mr. Carley explained that each test repellent was compared to the positive control (Ultrathon) and not to the untreated control. Dr. Chambers stated that the goal of the Board was to determine whether the CPT calculated for each product could be trusted, not to compare products.

Dr. Fisher questioned whether calculating CPT based on the shortest time period to a bite represented biting by the "odd" mosquito that bites earlier than the rest of the population. She summarized that the Board has determined that the study was "messy" but there was no evidence of residual effects from using repellents on the days prior to testing, no evidence of problems related to limb choice, and no evidence that the distance between test subjects had an effect. Differences in relative humidity, temperature, etc., may have had an effect, but performing the tests on different days provided some degree of control. There was insufficient power to perform ANOVA. Pooling of the subjects may have been problematic, the subjects were not properly randomized, there was no statistical independence, and error measurements were incorrect.

Dr. Kim stated that the results ignored independence because combining results from site 1 and 2 and subject overlap was not accounted for. This overlap and lack of independence renders the results un-interpretable. Dr. Lebowitz added that because of the pooling of data, lack of appropriate randomization, and other design flaws, he has concluded that the results are not scientifically sound. Dr. Fisher clarified that there are two questions to address regarding the scientific soundness of the results. The first pertains to the testing of repellents on successive days using the same subject, limb choice, and field conditions; these matters did not render the results unsound. She agreed that the pooling of subjects and other design issues raise questions about the scientific validity and interpretability of the results.

Dr. Brimijoin requested the Board consider whether they would reject this study because of flawed statistics. He agreed that the study was not optimal and was analyzed in ways that required unconfirmed assumptions. He asked the Board whether they believed that no meaningful conclusions could be drawn from the raw data or whether there were other ways to re-examine the data and draw reasonable conclusions. Dr. Kim responded that if the controls were correctly distributed over test days and sites, the data could be salvageable; however, the

data indicate that there was no control of allocation of subjects to sites, treatments, or dates. All assumptions needed to perform a trustworthy analysis of the data have not been met.

Dr. Lebowitz commented that his conclusion that the study was scientifically unsound was based on the pooling of subjects and confounding that could have occurred. Dr. Johnson remarked that Dr. Gupta has used crossover designs in his repellent test to control for differences among subjects. In this case, the subjects received all treatments, so the design was not balanced. Dr. Chambers countered that this was a field study and thus is not ideal. She asked Board members if they believed the results would be significantly different if the study had been designed differently. The study may not be statistically correct, but the data and conclusions likely are accurate. Dr. Gupta agreed that in field studies, it can be difficult to control for multiple variables. If treatments are performed appropriately, statistical methods can be used to infer missing data points, which may be possible to do for this study. Dr. Chambers asked if there was evidence that using a balanced design would significantly affect the data. Dr. Schofield answered that, in his experience, using a more robust statistical algorithm would not affect the final results. If environmental parameters were significantly different, random sampling would have a larger effect, but the major effects likely would be the same. Dr. Strickman stated that if the goal of the protocol was to draw comparisons between products, the design was insufficiently robust. The study is valid for estimating duration. The part of the design that is the most worrisome is that it was carried out over the course of an entire day. Biting activity increases in the evening, which could lead to a bias that underestimates duration because the mosquito population becomes more avid at the time that the repellents begin to degrade.

Dr. Sharp noted that the Board reviewed the protocol and study design and asked why Dr. Kim considered the data to be flawed. This would imply that the Board's recommendations were incorrect, or inappropriate changes were made in the implementation of the protocol. He asked whether it was consistent, given its earlier recommendations, for the Board to decide at this point that the data are unsound. Dr. Kim explained that at the January 2007 HSRB meeting, Dr. Alicia Carriquiry raised issues concerning the study design and these changes were not implemented by the investigator. The problems related to insufficient numbers of subjects also were raised. The problem with this protocol is that the distribution of subjects was performed incorrectly. If the experiment had been properly designed, imputations similar to those used by Dr. Gupta could be used to perform an appropriate analysis. The way this protocol has been performed, it is impossible to estimate errors or variance. Dr. Fisher asked if the estimation of duration was reliable. Dr. Kim answered that the data can be used to estimate duration, but not variability. Dr. Johnson agreed that error could not be measured. Dr. Chambers countered that estimating duration, not determining variability, was the goal of the experiment. If the data lead to a conservative estimate of duration, this would offer better protection for users.

Dr. Brimijoin commented that SCI-001 and WPC-001 are separate studies of multiple compounds, and data from these studies cannot be used to compare products. By chance, there were overlapping subjects between the two studies. It also is unfortunate that subjects were not equally distributed at the two sites. The protocols provide field data on duration of the products, with some indication of variability. Dr. Fisher clarified that the issue of pooling was discussed at the January 2007 HSRB meeting, and some of the Board recommendations were not

incorporated and there are indications of failure to adhere to the protocol. Mr. Carley stated that issues arising in the review of this study at this meeting were not in fact addressed at the January 2007 HSRB meeting, namely the issue of pooling data across studies. Dr. Lebowitz indicated that the Board recommended using 10 subjects per arm. Mr. Carley agreed, but added that the Board did not agree that 10 subjects per arm per day were needed. Dr. Philpott said that the Board raised comments about the statistical design of the protocols but concluded that, if followed, the protocol would generate scientifically valid data. It would not be inconsistent of the Board to conclude at this point that the data are not valid because an unexpected issue arose in the implementation of the protocols. Dr. Krishnan commented that this situation points to a lack of feedback; the Board makes recommendations, but does not know if they are implemented. He remarked that it was obvious that there were protocol deviations, some of which are attributable to environmental issues. Field studies should perhaps include a contingency plan to permit changes to the protocol that would still result in scientifically valid data. He said that the Board would have had questions if the issue of possible protocol deviations had been raised during the review of the protocol.

Dr. Fisher concluded that although there were errors (testing of subjects on successive days, choice of test limb) in the study, there is no evidence that these changed the outcome. The overlap of subjects and pooling of data means that the data is not legitimate for comparison of products. The data might be useful for estimating duration of efficacy, but the calculations of standard deviation are questionable. The data likely provide a conservative estimate of CPT.

Ethical Considerations – SCI-001

Dr. Philpott opened discussion of ethical considerations for the protocols. Because the studies were conducted concurrently, finding that one study was conducted unethically may apply to the datasets of both. If the Board recommends that EPA cannot use the data from SCI-001 because of protocol violations, this may imply that data from WPC-001 also cannot be used. Dr. Philpott commended Mr. Carley on his summary of the data across the two studies. He agreed with Mr. Carley that the most significant protocol deviations include serological testing of captured mosquitoes, changes in the exclusion criteria, and testing of LipoDEET 3434 without notifying the IIRB.

Changing the protocol to include serological testing of mosquitoes should have been submitted to the IIRB, but because it is likely to increase protection of subjects, this is not a serious violation. The analyses also were performed independently; if the analysis had been performed by Dr. Carroll, Dr. Philpott would not have expected this change to be presented to the IIRB. The other violations—changing the exclusion criteria and using LipoDEET 3434—are more serious violations. The Board must decide if these violations placed the subjects at greater risk of harm or compromised the informed consent process to an extent that the Board must decide that the data cannot be used. Dr. Philpott expressed disappointment at the degree of protocol violation, especially because failure to inform the IIRB of protocol changes has occurred previously. This raises the question of whether Dr. Carroll is aware of proper human protection procedures.

Dr. Sharp agreed that he, too, was disappointed by the protocol violations. A number of subjects volunteered for a study that they believed would provide sound information. The validity of the results has been compromised, which means the subjects may have been asked to make sacrifices that were not warranted. The departure from the stated exclusion criteria should have been reported to the IIRB and is a substantial deviation. This deviation may not have changed the risk-benefit assessment, but this is IIRB's decision to make, not the Board's or Dr. Carroll's.

Concerning use of LipoDEET 3434, regulations state that before intentional exposure studies take place, the study must be reviewed by the Board. The Board did not review use of LipoDEET 3434 and thus this data cannot be used by EPA. The implications of this for WPC-001 are unclear.

Dr. Menikoff agreed with Drs. Philpott and Sharp. He stated that he was less concerned about inclusion of serological analyses and changing the exclusion criteria, but the use of LipoDEET 3434 is troubling. The purpose of the Board is to assess exposure to test compounds. Most are benign, but Congress has mandated review of intentional exposure. The Board thus cannot conclude that this protocol was in substantial compliance with regulations.

Mr. Carley explained that inclusion of LipoDEET 3434 affected 66 of 100 data points across the two studies, but that assumed the data points from subjects who received LipoDEET 3434 were dropped. Dr. Fisher noted that in IRB applications, the principal investigator signs a statement agreeing not to make any changes to the protocol without IRB approval. Dr. Philpott stated that although this may not appear to be a significant violation because the compound is similar to other, approved formulations, it is a serious violation of both the intent and letter of the regulations; ethically, EPA cannot use this data. Because of the randomization and integration of all compounds into a single protocol, none of the SCI-001 data can be used. Dr. Menikoff agreed that none of the data of any subjects who had a chance of being randomized to the unapproved compound can be used because one of the arms they could have been assigned to was not approved. This includes any subject who consented to participate in SCI-001.
Dr. Brimijoin asked if the data from WPC-001 also may be unusable, because there was overlap between subjects participating in each protocol. Dr. Philpott said this was likely to be the case if subjects participating in both studies signed both informed consent forms. Dr. Fisher concluded that there was unanimous agreement that SCI-001 was not in compliance with 40 CFR part 26, subparts K and L.

Scientific Considerations – WPC-001

Dr. Chambers stated that her science assessment of WPC-001 was the same as that for SCI-001. The residual effects of successive days of testing were unlikely to have had an effect (CPTs were shorter) and the data therefore is useable. Drs. Lebowitz and Lehman-Mckeeman agreed. Dr. Lehman-Mckeeman commended Mr. Carley's organization of the data, which assisted the Board's review. Treatment of subjects on successive days is not intellectually satisfying, but it was unlikely to have a significant effect.

Ethical Considerations – WPC-001

Dr. Philpott opened the ethics discussion of WPC-001. Because WPC-001 and SCI-001 were conducted in the same location and used overlapping subjects, the issue is how the data from WPC-001 can be used, given the deficiencies of SCI-001. There are issues related to the consent process because of unusually dated consent forms. Even investigators developing the most ethical and organized studies make mistakes, and the question is whether this was a consistent pattern and whether it impacted subject risk and the consent process. Limb measurements of some subjects were taken before they signed the consent forms; Dr. Philpott did not condone this, but it was not a significant deficiency. The decision not to adhere to the 24-hour exclusion criterion should have been reported to the IIRB before the study was initiated. This deviation probably did not place subjects at increased risk, but did impact the informed consent process.

Dr. Sharp noted that it was important to distinguish between the two protocols. The change in test compounds was not an issue for WPC-001. The departure from the exclusion criteria is a major unresolved issue that cannot be fully evaluated until the Board receives IIRB's response to this violation. The IIRB has the authority for judging whether these deviations are serious. Dr. Fish agreed with the issues raised by Drs. Philpott and Sharp. Dr. Fisher agreed that it was problematic that the exclusion criterion in the informed consent form was violated. She added that the fact that this violation has not yet been submitted to the IIRB also is troubling. Although authority for judging this deviation lies with the IIRB, the Board can comment on Dr. Carroll's role in the protocol violation. Dr. Sharp asked whether the Board can disagree with the IIRB concerning the seriousness of this violation. Dr. Fisher answered that the Board can disagree with the IIRB and its judgments are not dependent on those of IRBs. She asked whether the Board believed that the protocol violations rise to the level of substantial noncompliance. Dr. Philpott explained that if the Board makes recommendations concerning deficiencies in the protocol, the Board must define its deficiency criteria, such as risk and impact on the informed consent process. His opinion was that these were major violations, but whether changing the exclusion criterion affected the participants' understanding of the risks and benefits of participation is in question. Mr. Carley clarified that the informed consent form did not indicate that participants would have 24 hours between testing, but rather that to be eligible, participants must refrain from using repellents 24 hours before initiation of the protocol. Dr. Philpott remarked that he does not believe that this violation affected the informed consent process to a degree that the Board must conclude that EPA cannot use the data. Dr. Sharp countered that the protocol is not in compliance with the IRB-approved protocol and 40 CFR part 26 demands such compliance. Dr. Philpott noted that the regulations require the protocol to be "substantially compliant." Mr. Carley clarified that the regulations address the idea of changes to approved research only in the context that changes without approval do not happen. The principal investigator signs a statement in the IRB application indicating he will not change the protocol without IRB approval. This is the basis from which to judge compliance. Dr. Fisher indicated that she was troubled that this issue has arisen previously for this investigator, such that the HSRB recommended that he take an ethics course. The regulations state that if ethical violations occur but the data is important to protect the public, the data can be used; however, this data is not critical for protecting the public. Dr. Fitzpatrick disagreed with Dr. Fisher because Dr. Carroll could have interpreted the exclusion factor differently. Dr. Lebowitz noted that the Board may need to read the response from IRB before making a final decision.

Mr. Carley requested clarification on the impact of the overlap between WPC-001 and SCI-001. Only two data points at each site of the WPC-001 protocol are independent of SCI-001 concerns. Dr. Philpott stated that because participants were individually consented for each study, this creates a wall between the studies. Although only four subjects participated in WPC-001 but not in SCI-001, participation in the two studies can be considered as separate, despite overlapping days of testing. Dr. Fish noted that the consent form prohibited use of repellents 24 hours prior to initiation of the study. If the initiation of the study was the dosimetry phase, and then testing occurred on consecutive days, this would be consistent with what a participant would understand.

Dr. Fisher summarized that it was unclear whether violation of the consent process occurred, given the possible different interpretations of the exclusion criterion. The overlap between SCI-001 and WPC-001 was not problematic because subjects independently consented to participate in each study. Regarding the exclusion criterion change, because Dr. Carroll did not believe this increased risk for the participants, he did not believe this change needed to be reported to the IIRB. He also has not yet reported the change to the IIRB. These are not substantial violations.

Dr. Parkin discussed the use of experienced subjects to assist with application of the repellents. Mr. Carley explained that pre-identified subjects served as untreated controls. Within that group of experienced subjects, those serving as controls were asked to assist with dosing to allow more consistent timing of dosing. His concern was that dosing by skilled technicians was considered as a risk minimization factor and asked whether risk to subjects was changed because other subjects performed the dosing. The informed consent form does not discuss this issue. Dr. Parkin stated that one subject dosing another subject is a serious concern. Dr. Fisher disagreed, but asked whether this should have been included in the informed consent form and whether it increased risk or violated the consent process. Dr. Fitzpatrick noted that the control subjects may have been skilled technicians, but not employees of Dr. Carroll. Dr. Chambers indicated that because dosing was non-invasive, this change was trivial. Dr. Fisher summarized that this was an important change, but did not rise to the level of substantial noncompliance. Mr. Carley remarked that this change in the role of subjects appeared to be at least as serious a violation as the change in the exclusion factor. Mr. Jordan explained that the protocol described a process, the IIRB reviewed and approved the protocol, the Board and EPA reviewed and approved the protocol, and subjects consented to participate, but then the investigator asked the subjects to perform a different activity. He stated that this was troubling. This particular situation did not alter risk, but does depart from the IRB and review process that is intended to ensure that the investigator always acts in the best interest of the participant. Dr. Sharp agreed with Mr. Jordan. Each violation is a relatively minor compliance issue that should have been reported to the IIRB, but none rise to the level of substantial lack of compliance; however, taken together, the violations should make the Board uncomfortable. Dr. Fisher stated that the Board was initially sympathetic to the newness of the process and its role in educating investigators. Dr. Menikoff asked to what extent these violations are the result of confusion or misunderstanding. Application of mosquito repellent is not a skilled technique and using control subjects to apply the repellent likely did not increase risk.

Dr. Chadwick explained that he expected these protocols to achieve a high standard if they are submitted for regulatory purposes. It is not the role of the investigator to determine the effect of change on the risk-benefit analysis. He agreed that these individual violations were not substantial, but the changes should have been discussed with the IIRB. This is the same ethical deficiency as failure to notify the IIRB of the change in test products. Failure to report the changes to the IIRB deprived the IIRB of its chance to exercise appropriate oversight. Dr. Fitzpatrick noted that the informed consent form does not indicate who would apply the repellent and thus is not a protocol violation. Mr. Carley clarified that the protocol stated that repellents would be applied by Carroll-Loye Biological Research technicians. Dr. Fisher agreed with Dr. Chadwick's observation concerning the consistency in the lack of alerting the IIRB to changes in the protocol. She stated that the Board must be cautious about appearing to communicate that investigators can make changes without informing the IRB and the Board will decide subsequently whether or not the changes were dangerous. She asked whether the failure to report the two changes to the IIRB rose to the level of substantial noncompliance. Dr. Philpott explained that the ethics reviewers are troubled by the lack of compliance. Given this and the HSRB's role in setting precedence, he suggested that the Board should consider deciding that EPA cannot use the data. Dr. Menikoff added that the change in the exclusion criterion could have been a miscommunication. He stated that Dr. Carroll could have plausibly believed that no change was made to the protocol. Regarding application of the repellent by untreated controls, this is a minor change and if the Board decides that it rises to the level of noncompliance, the Board would be unable to approve use of data from any studies because changes in protocols occur frequently. These changes are minor compared to the use of the unapproved test compound. He commented that it would be inconsistent to decide that these data cannot be used because of the change in repellent application procedure.

Dr. Fisher suggested that the Board's report state that there were violations of specific requirements but consensus was not reached concerning whether these rose to the level of substantial noncompliance. Dr. Sharp stated that the failure to report changes to the IRB was a judgment error that likely will be seen for other protocols. The failure to disclose these changes does not rise to the level of substantial noncompliance. Dr. Brimijoin agreed that the Board was not in danger of sending a mixed message concerning what sort of violations constitute substantial noncompliance. Dr. Philpott disagreed, particularly because he was troubled by the historical pattern of failures to inform the IIRB of changes and was cautious about setting a precedent that appeared to indicate that some degree of noncompliance was acceptable. Dr. Fisher summarized that the report would indicate that the Board agreed that Dr. Carroll's failure to report changes to the IIRB were ethical violations; however while a majority of the Board agreed that these violations did not rise to the level of substantial noncompliance, some Board members believed it did meet that level.

EPA Review of Carroll-Loye Biological Research Protocol SPC-001

Introduction

Mr. Carley provided background on protocol SPC-001. Carroll-Loye Biological Research submitted protocol SPC-001 on July 18, 2007. SPC-001 proposes a field study of mosquito repellent efficacy of three test repellents, all containing picaridin as the active

ingredient: EPA Reg No 121-89 (7-percent pump spray), EPA Reg No 121-91 (15-percent pump spray), and an unregistered lotion with 15 percent picaridin and sunscreen. EPA requires efficacy data to support label claims for this registrant's picaridin products as a condition of continued registration. EPA has agreed that results of testing the 7-percent and 15-percent pump sprays can be extrapolated to support the registrant's other spray and wipe-on products which contain similar concentrations of picaridin and similar non-pesticidal ingredients. EPA requires product-specific testing to support the pending application for registration of the lotion containing both picaridin and sunscreen.

SPC-001 is similar to other Carroll-Loye protocols for field mosquito repellency studies previously reviewed by the HSRB. The initial submission meets the standard of completeness defined in 40 CFR §26.1125. EPA's science and ethics review of September 24, 2007 was based on the initial protocol submission, which has not been amended. The few deficiencies noted in EPA's review can easily be corrected and thus this protocol is ready for HSRB review.

This is a proposal for research involving intentional exposure of human subjects, with the intent to submit the resulting data to EPA under FIFRA. Applicable regulatory requirements are 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.

Scientific Considerations

Mr. Sweeney presented EPA's science review of SPC-001. The objectives of this study are to test the mosquito repellent efficacy characteristics of the test materials, satisfy a condition of continued registration imposed by EPA on the registrant's conditionally registered picaridin products, and support the pending registration of the lotion product.

The dermal NOAEL reported by WHO for picaridin is 5,000 mg/kg. Assuming a dose of 1 gram (g) per 600 square centimeters (g/cm^2), the MOE for the 15-percent spray is greater or equal to (≥) 1,000 (the actual dose is likely to be lower). MOEs for the 7-percent spray and the 15-percent lotion would be higher, because the 7-percent spray contains less picaridin and the 15-percent lotion contains no ethanol.

The dosimetry phase will be performed using 10 subjects to establish the typical consumer dose of each formulation for use in efficacy testing. The dosimetry phase results will be shared with protocol SPC-002. Subjects will be trained in the laboratory to aspirate landing mosquitoes before they bite, using laboratory-reared, pathogen-free mosquitoes. Because the lotion and spray treatments are easily distinguishable, the study is not blinded. The protocol calls for 10 subjects treated with each formulation and 2 untreated control subjects to participate in each of 2 field trials. The sample size of 10 is justified in the protocol based on arguments considered by the HSRB in previous reviews of similar Carroll-Loye protocols. Given the Board's comments from previous HSRB meetings, EPA is reconsidering this matter in general. EPA believes a sample size of 10 treated subjects, substantially exceeding the size specified in the current draft guidelines, is acceptable for studies of this type.

Untreated subjects will monitor mosquito pressure; each will be attended by 2 technicians to aspirate mosquitoes before they can probe or bite. To determine product efficacy, both treated and untreated subjects will be exposed to mosquitoes for 1 minute at a time every 15 minutes until efficacy failure. Duration of efficacy (CPT) for each subject will be measured as the time from treatment to "first confirmed landing with intent to bite" or "FCLIBe."

Testing will be performed at field sites located in the California Central Valley or Southern California, depending on the season. The sites must have had no reported WNV activity for at least a month before field testing. Expected wild mosquito populations are *A. vexans, e. melanimon, A. taeniorhynchus, C. tarsalis,* and *C. pipiens*, and possibly other mosquito species that are found in the same habitats.

Measured variables will be subject limb area, weight of test materials delivered to dosimetry subject's limb (lotion) or gauze dosimeters (spray), mosquito pressure (must be $\geq$ 1 landing per minute) and time to FCLIBe. The mean time to FCLIBe, with standard deviation and 95 percent confidence interval, will be calculated across all subjects at each site. Median time to FCLIBe will also be calculated using Kaplan-Meier survival analysis.

A deficiency in the protocol is failure to adequately characterize the composition of the lotion product, although this is fully described in the application for registration. This protocol is likely to yield scientifically reliable information, satisfying scientific criteria from the framework recommended by the HSRB, namely that it would produce important information that cannot be obtained except by research with human subjects, has clear scientific objectives and an explicit hypothesis, and the study design should produce adequate data to achieve those objectives and test that hypothesis.

Ethical Considerations

Mr. Carley presented EPA's ethics assessment of SPC-001. This study proposes to test the mosquito repellent efficacy of three test formulations in the field. Two of the test formulations are conditionally registered; field efficacy testing is required to fulfill a condition imposed on the registrations and to keep the products on the market. The third test formulation is a candidate for registration, and testing is required to support proposed label claims. Demonstration of field efficacy for the test products would keep them on the market or make available alternatives to other mosquito repellents, some of which are found unpleasant by many users.

Subjects will be recruited from among "subjects . . . in previous Carroll-Loye repellent efficacy tests [who] have agreed or requested to be in our Volunteer Database." Exclusion factors are anyone under 18 or over 55 years of age, students or employees of the investigator, pregnant or nursing women, those sensitive to repellents or to mosquito bites, those in poor health or physical condition, and those unable to speak and understand English. Two "experienced" subjects will serve as untreated controls in each field trial. No eligible subjects are members of populations vulnerable to coercion or undue influence.

The test repellents are harmful if swallowed. Other risks to subjects include eye irritation if the test repellents contact the eye, possible exposure to biting arthropods, and possible exposure to arthropod-borne disease. The protocol does not discuss risks of embarrassment or other psychological risks associated with mandatory pregnancy testing of female candidates, although the research design effectively minimizes these risks. Risks from test material are minimized by excluding sensitive candidates, monitoring the dosimetry phase closely, and having the repellent applied by a technician. Risks from mosquito bites are minimized by excluding sensitive candidates, training subjects to aspirate mosquitoes before they have time to bite, and minimizing exposure of skin. Risks of disease are minimized by conducting research where no mosquito-borne viruses have been detected for at least a month, by minimizing bites, and by testing aspirated mosquitoes for pathogens. The probability of harm is characterized as "extremely small" because of the low acute and chronic hazard profile of the products, the design of the research to minimize exposures, training subjects to aspirate landing mosquitoes before they have time to probe or bite, and field testing in areas free of mosquito-borne viruses for at least a month.

There are no direct benefits for the subjects; the primary direct beneficiary is the sponsor. If the materials are proven effective and remain on or enter the market, indirect beneficiaries will include repellent users who prefer one of these products to other mosquito repellents. EPA has concluded that no reasonable opportunities to further reduce risk while maintaining scientific robustness have been overlooked, residual risks to subjects are very low, and the risks to subjects are reasonable in light of the expected societal benefits to repellent users, which are likely to be realized.

The IIRB of Plantation, FL reviewed and approved the protocol and informed consent materials on July 17, 2007. This IRB is independent of the sponsors and investigators, registered with Office for Human Research Protections (OHRP), and not accredited by Association for the Accreditation of Human Research Protection Programs (AAHRPP). IIRB procedures are reported not to have changed since previous submission to EPA; EPA has previously determined they meet regulatory standards. The protocol's description of subject recruiting and consent processes is complete and satisfactory. Separate recruitment processes were established for treated and untreated subjects, as well as separate IRB-approved consent forms. The consent forms do not address risks linked to pregnancy testing. Methods proposed for managing information about prospective and enrolled subjects will protect their privacy. The subjects will be free to withdraw at any time, and will be reminded of this at several points. Medical care for research-related injuries will be provided at no cost to the 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 this research are 40 CFR part 26, subparts K and L. A point-by-point evaluation of how this protocol addresses the requirements of 40 CFR part 26, subparts K and L and the additional criteria recommended by the HSRB appears as Attachment 1 to the EPA Review of September 24, 2007.

To address noted deficiencies, EPA has recommended that a data collection form suitable for recording the field efficacy testing should be added to the forms set provided in the protocol.

The approved product labels for the registered test materials, and the proposed label for the lotion still pending registration, should be attached to the protocol and made available to the subjects in the dosimetry phase, so the label directions can guide their self-treatment with a "typical consumer dose." If these deficiencies are corrected, SPC-001 meets all requirements of §26.1111, §26.1116, and §26.1117, all requirements of §26.1125, and all requirements of §26.1203. If further revised to correct the few remaining deficiencies, protocol SPC-001 will meet the applicable requirements of 40 CFR part 26, subparts K and L.

The Board is asked to consider if the proposed research described in protocol SPC-001 from Carroll-Loye Biological Research, revised as suggested in EPA's review, appears likely to generate scientifically reliable data, useful for assessing the efficacy of the test substances for repelling mosquitoes and if the research appears to meet the applicable requirements of 40 CFR part 26, subparts K and L.

Dr. Philpott asked if the Board has the information it had previously requested concerning the membership, background, and training of members of this IRB. Mr. Carley answered that EPA would like more information about the qualifications and accreditation of the IIRB, but does not currently have this information. EPA and the HSRB have lists of members and their educational backgrounds.

Public Comments

Dr. Fisher invited oral public comment on protocol SPC-001. No oral public comments were received.

Board Discussion

Scientific Considerations – SPC-001

Dr. Chambers opened the science discussion of SPC-001. She noted that deficiencies related to information about the lotion formulation have been addressed. She expressed concern about using data from the tested products to extrapolate for other products. Extrapolating information from the 7-percent pump spray to a 10-percent pump spray formulation is acceptable. She expressed doubts about extrapolating from the 7-percent pump spray to the 5.75-percent towelette because the towelette may not administer the same dose; however, if the dosimetry phase demonstrates the towelette administers approximately the same dose, extrapolation would be acceptable. Dr. Krishnan stated that this assessment was similar to that concerning SCI-001, namely that the statistical analysis of the data generated from this protocol will be an issue.

Dr. Johnson referred to the listing of subjects and their assignments to test substances on page 14 of the protocol. According to this list, 32 different subjects will participate in the study. Dr. Johnson stated that based on his experience, this is not acceptable. He requested a list of which subjects are treated with which products on which days, to avoid the problems that arose with protocol SCI-001. Dr. Fisher asked if Dr. Johnson believed that the Board could not adequately analyze this protocol without this information. She reminded the Board that it is not the Board's role to design studies, but asked if the discussions related to other protocols

suggested that the Board should have further information on study design before reviewing protocols. Dr. Fish questioned whether, given the information presented by the consultants concerning the variability of field studies, a cross-over design would help control for this variability. Dr. Johnson indicated that he would not specify a design, but the protocols should have more information on the design and how it was chosen. Dr. Fisher remarked that one option was to decide that the Board cannot review this study at this time because more information on study design is needed. She noted that the discussions occurring early in the October 25, 2007 session might provide guidance concerning information the Board needs to perform an adequate review.

Dr. Chambers expressed concern that the Board's demands are not feasible for field studies, which require flexibility to make changes because of variable conditions. Dr. Johnson interjected that Dr. Gupta had presented information suggesting that field experiments for repellency can be well designed; deviations may occur, but the underlying structure or plan remains valid. Dr. Fisher inquired if the purpose of this protocol was to estimate duration of repellency or generate comparisons between products. Mr. Carley explained that the purpose of this experiment was only to generate CPTs for each product; no comparisons between products will be made. Dr. Parkin suggested that changes occurring in field research can be managed ahead of time by determining which factors most affect risk. Alternative plans can be developed which would obviate the need to return to the IRB if these changes need to be made.
Dr. Johnson commented that if this protocol will actually consist of three different experiments, a separate protocol for each product could be developed. If the products will not be compared, randomization is less of an issue if the experiments can be performed on separate days.
Mr. Carley agreed that randomization and allocation of subjects to treatments needs to be fully specified.

Dr. Fisher summarized that the Board is not comfortable recommending that the protocol would generate scientifically reliable data, largely to avoid the problems that arose upon review of the completed protocol SCI-001. Dr. Lebowitz agreed that, in light of the discussion of SCI-001, the Board is not prepared to evaluate this protocol and decide if it would provide scientifically sound data.

Ethical Considerations – SPC-001

Dr. Philpott opened discussion of the ethics of SPC-001. He agreed with Mr. Carley's ethics assessment. The three primary risks to subjects are from the products, mosquito bites, and vector-borne disease. Risks from the products are low because two of the products and the active ingredient are previously registered. Risks from bites are minimal because subjects are trained to aspirate landing mosquitoes, subjects will work in pairs to minimize bites, bites can be easily treated with over-the-counter remedies, and people with sensitivity to bites are excluded. Use of seminal flocks, vector surveillance and post-test analyses of captured mosquitoes will minimize risk of vector-borne illness. The exclusion criteria are appropriate and adequate stopping rules and medical plans are in place. The risk of embarrassment associated with pregnancy testing should be mentioned. The risks of participation in this protocol have been adequately minimized and the benefit to society outweighs the risks.

Dr. Sharp asked Mr. Carley to communicate to the investigator that the Board has not faulted the investigator for the content of the design or the informed consent form. The Board's criticism focuses instead on the communication between the investigator and the IRB. Dr. Fish added that the HSRB has not yet received additional information it requested on the IIRB.

EPA Review of Carroll-Loye Biological Research Protocol SPC-002

Introduction

Mr. Carley provided background on protocol SPC-002. This protocol was submitted on July 18, 2007, and proposes a laboratory study of tick repellent efficacy of three test repellents, all containing picaridin as the active ingredient. The three test repellents are EPA Reg No 121-89 (7-percent pump spray), EPA Reg No 121-91 (15-percent pump spray), and an unregistered lotion with 15 percent picaridin and sunscreen. SPC-001 is similar to other Carroll-Loye protocols for laboratory tick repellency studies previously reviewed by the HSRB. The initial submission meets the standard of completeness defined in 40 CFR §26.1125. EPA's science and ethics review of September 24, 2007 was based on the initial protocol submission, which has not been amended. The few deficiencies noted in EPA's review can easily be corrected and EPA believes this protocol is ready for HSRB review.

This is a proposal for research involving intentional exposure of human subjects, with the intent to submit the resulting data to EPA under FIFRA. The applicable regulatory requirements are 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.

Scientific Considerations

Mr. Sweeney presented EPA's science review of SPC-002. The objectives of this study are to test the tick repellent efficacy of the test materials, satisfy a condition of continued registration imposed by EPA on the registrant's picaridin products, and support the pending registration of the lotion product.

The dermal NOAEL of picaridin, as reported by WHO, is 5,000 mg/kg. Assuming a 1 g/600 cm^2 dose, MOE for the 15-percent spray is ≥1,000; the actual dose is likely to be lower. The MOEs for the 7-percent spray and the 15-percent lotion would be higher, because the 7-percent spray contains less picaridin and the 15-percent lotion contains no ethanol. The dosimetry phase will involve 10 subjects and is performed to establish the typical consumer dose of each formulation for use in efficacy testing. The dosimetry phase results will be shared with SPC-001. The standard dose rate will be converted to subject-specific dose based on measured skin area of forearm to be treated and the subject-specific dose will be applied by a technician.

Laboratory-reared and pathogen-free deer ticks (*Ixodes scapularis*) and American dog ticks (*Dermacentor variabilis*) will be used. Subjects are trained in the laboratory to handle and observe ticks, and to remove them before they can bury or bite. After a single use each tick is destroyed. Before use in a repellency trial, each tick must demonstrate normal questing behavior.

To qualify the ticks, each subject will serve as his or her own control to verify attractiveness to each tick before using it in the repellency trial. The subject places the hand of the untreated arm on a laboratory bench, and holds the arm upright. Every 15 minutes a fresh tick is placed on a mark near the subject's wrist; normal ticks will move upward, seeking a site at which to bury and bite. Ticks that move at least 3 centimeters (cm) toward the elbow on a subject's untreated arm within 3 minutes qualify for repellency testing on the treated arm.

To test repellency, a newly qualified tick is placed on a mark 3 cm below the treated area on the subject's wrist every 15 minutes. If the tick fails to cross at least 3 cm into the treated area within 3 minutes, it is scored as a repulsion. If the tick crosses at least 3 cm into the treated area within 3 minutes, it is scored as a crossing. A crossing followed by another crossing within either of the subsequent 2 exposure periods is considered a "confirmed crossing."

Measured variables include subject limb area, weight of test materials delivered to the dosimetry subject's limb (lotion) or gauze dosimeters (spray), questing behavior of ticks, response of each qualified tick to repellent, and time to all tick crossings. Duration of efficacy (CPT) for each subject will be calculated as the time from treatment to "First Confirmed Crossing" (FCC) into treated area. The mean time to FCC across all subjects, with standard deviation and 95 percent confidence interval, will be calculated for each test material. Median time to FCC for each test material will also be calculated using Kaplan-Meier survival analysis.

Ten subjects treated with each formulation will participate in the repellency trials. The sample size of 10 is justified in the protocol by arguments considered by the HSRB in previous reviews of similar Carroll-Loye protocols; EPA is reconsidering this matter in the general case. At this point, EPA believes a sample size of 10 treated subjects, substantially exceeding the size specified in the current draft guidelines, is acceptable for studies of this type.

Deficiencies include inadequate characterization of the composition of the lotion product in the protocol (although it is fully described in the application for registration). In addition, more care is needed to ensure ticks are pathogen-free because the American dog tick, *Dermacentor variabilis*, is a vector of Rocky Mountain Spotted Fever (RMSF), which can be transmitted from one tick generation to another transovarially. The study design makes the likelihood of a tick bite quite low, but assurance is needed that the ticks are RMSF-free, should a subject be bitten. The protocol also should clarify the action to be taken in the unlikely event of a tick bite.

EPA has concluded that this protocol is likely to yield scientifically reliable information, satisfying the scientific criteria from the framework recommended by the HSRB, namely that the protocol would produce important information that cannot be obtained except by research with human subjects, has clear scientific objectives and an explicit hypothesis, and the study design should produce adequate data to achieve those objectives and test that hypothesis.

Ethical Considerations

Mr. Carley provided EPA's ethics review of SPC-002. The proposed study would test the repellent efficacy of three test formulations in the laboratory against deer ticks and American

dog ticks. Two test formulations are conditionally registered; submitting product-specific field efficacy testing is a condition imposed on the registrants to keep the products on the market. The third test formulation is a candidate for registration, and testing is required to support proposed label claims. Demonstration of efficacy for the test products would keep or make available alternatives to other tick repellents, some of which are found unpleasant by many users.

Subjects will be recruited from among "subjects . . . in previous Carroll-Loye repellent efficacy tests [who] have agreed or requested to be in our Volunteer Database." Exclusion factors are anyone under 18 or over 55 years of age, students or employees of the investigator, pregnant or nursing women, those sensitive to repellents or phobic to ticks, those in poor health or physical condition, and those unable to speak and understand English. No eligible subjects come from populations vulnerable to coercion or undue influence.

Risks include irritation if the repellents contact the eyes and harm if swallowed. There is a potential risk of tick bites. The protocol does not discuss risks of embarrassment or other psychological risks associated with the requirement for pregnancy testing of female candidates, although the research design effectively minimizes these risks. The risks from test materials are minimized by excluding sensitive candidates, monitoring the dosimetry phase closely, and having a technician apply the repellent. Risks from tick bites are minimized by excluding phobic candidates and by training subjects to handle and observe ticks and remove them before they can bury or bite. Risks of disease are minimized by using pathogen-free laboratory-raised ticks, and by unspecified "measures . . . to make sure that ticks are removed before they have an opportunity to bury in the skin." The probability of harm is characterized as "extremely small" because of the low acute and chronic hazard profile of products, design of the research to minimize exposures, training subjects to handle and observe ticks and to remove them before they have time to bury or bite, and the use of pathogen-free laboratory-reared ticks.

There are no direct benefits for the subjects; the sponsor is the primary direct beneficiary. If the materials are proven effective and remain on or enter the market, indirect beneficiaries will include repellent users who prefer one of these products to other tick repellents. EPA has determined that no reasonable opportunities have been overlooked to further reduce risk while maintaining scientific robustness. The residual risks to subjects are very low and are reasonable in light of the expected societal benefits to repellent users, which are likely to be realized.

The IIRB of Plantation, FL reviewed and approved the protocol and informed consent materials on July 17, 2007. This IRB is independent of the sponsors and investigators and registered with OHRP, but is not accredited by AAHRPP. IIRB procedures have not been reported to have changed since previous submissions to EPA; EPA has previously determined they meet regulatory standards. The protocol description of subject recruiting and consent processes is complete and satisfactory; however, the consent form needs expansion to address the risk of tick bites and the risks associated with pregnancy testing. The consent form also should explain measures to ensure ticks are removed before they can bury and bite. The methods proposed for managing information about prospective and enrolled subjects will protect their privacy. Subjects will be free to withdraw at any time, and will be reminded of this at several points and medical care for research-related injuries will be provided at no cost to the 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 this research are 40 CFR part 26, subparts K and L. A point-by-point evaluation of how this protocol addresses the requirements of 40 CFR part 26, subparts K and L and the additional criteria recommended by the HSRB appears as Attachment 1 to the EPA Review of September 24, 2007.

EPA has noted several deficiencies. A data collection form suitable for recording the actual efficacy testing should be added to the forms set provided. The approved product labels for the registered test materials, and the proposed label for the lotion still pending registration, should be included in the protocol and made available to the subjects in the dosimetry phase, so the label directions can guide their self-treatment with a "typical consumer dose." The risks of tick bites and of exposure to tick-borne disease, mentioned in the protocol, should also be addressed in the consent form. The measures to ensure that ticks do not bury and bite, and by whom they would be implemented, are not explained.

SPC-002 meets all requirements of §§ 26.1111 and 26.1117, §26.1125, and §26.1203. The consent form needs expanded discussion of risks and more explanation of proposed measures to ensure ticks do not bury or bite to meet requirements of §26.1116. If further revised to correct remaining deficiencies, protocol SPC-002 will meet the applicable requirements of 40 CFR part 26, subpart K and L.

The Board is asked to determine whether the proposed research described in protocol SPC-002 from Carroll-Loye Biological Research if revised as suggested in EPA's review appears likely to generate scientifically reliable data, useful for assessing the efficacy of the test substances for repelling ticks and appears to meet the applicable requirements of 40 CFR part 26, subparts K and L.

Dr. Philpott clarified that alternate subjects are proposed to protect privacy issues associated with pregnancy testing. Dr. Fish noted that WNV is a greater risk for people over 55 years of age, and asked why these people had been excluded from the study, given that the ticks are laboratory-raised. Mr. Carley agreed that the concern about the increased susceptibility of those over 55 years of age does not apply to this protocol; however, the pool of volunteers contains no, or very few, people older than 55 years of age.

Public Comments

Dr. Fisher invited oral public comment on protocol SPC-002. No oral public comments were received.

Board Discussion

Scientific Considerations – SPC-002

Dr. Chambers opened the science discussion of SPC-002. She noted that it was similar to other protocols submitted by this investigator. She indicated more information on the lotion,

including its Sun Protection Factor was needed. She expressed continued concern about extrapolation of the results to the towelette formulation because of differences in application, which could alter the dose; however, this applies to interpretation of the results and not the protocol itself. Because this is a laboratory-based study, it is more easily controlled and statistical designs will be more easily implemented. Dr. Fisher inquired how important the ability to extrapolate the data was for this study. She asked whether the Board should provide a recommendation concerning this matter, if the dosimetry phase shows that the doses are significantly different. Dr. Chambers suggested recommending that the data not be extrapolated if the doses are different. Mr. Carley remarked that EPA would suggest to the investigator that he add the towelette to the dose phase to determine if it delivers a similar effective dose. If not, he would need to add the towelette to the study.

Dr. Lebowitz continued the discussion and noted that information was needed that would specify the way subjects are allocated to treatments. He commented on the lack of a positive control for the vehicle of the formulations. There is no blinding in the current design, but this could have been included. There is no explicit control for relative humidity and temperature or other sources of variability. Use of local volunteers may not be representative of the U.S. population. The investigator contends that individual differences in repellent performance and subject attractiveness to ticks will not strongly impact the data and thus representativeness and generalizability are sound; however, this is not clear. If the protocol is sufficiently revised to address the deficiencies noted by EPA, the protocol appears likely to generate scientifically useful data. Dr. Fitzpatrick agreed with Drs. Chambers and Lebowitz and declined to add to the discussion.

Dr. Kim noted that this study had problems similar to those found in SPC-001. Because SPC-002 is a laboratory-based study, it should be easier to solve these problems. The protocol calls for "partial randomization," but it is not clear exactly what this means. Subjects are assigned based on a randomly assigned number, but the protocol also states that subjects may test more than one repellent on separate days; this implies overlap among subjects that could create problems. If overlap occurs, an appropriate study design is needed to permit drawing of proper statistical inferences.

The specific language in the section on statistical analyses is incorrect regarding Kaplan-Meier analysis. Direct comparison cannot be drawn between Kaplan-Meier analysis and mean and 95 percent confidence interval. Because of censoring, the values are different. The median of a Kaplan-Meier analysis is less sensitive to censoring. There are minor errors in instructions in the protocols, for example, mention of "mosquito" instead of "tick", and some discrepancies in the MSDS. There is overlap of product item numbers and there appears to be differences in EPA registration numbers.

Quantification of efficacy using normal theory provides an inadequate mean and confidence interval if there is censoring of the time to efficacy failure. Because no comparisons will be made between products, power is not an issue. There is no statistical justification for sample size. Because similar protocols have been submitted previously, the investigator should have some idea about the likely variability and should use this to justify sample size.

Dr. Fisher summarized that justification of sample size was needed and variability of laboratory conditions (humidity, temperature, etc.) needs to be addressed. The statement concerning "partial randomization" should be clarified. There appear to be inconsistencies in the protocol's discussions of randomization. She questioned whether it was also premature for the Board to assess this study, or if the fact that it is a laboratory-based study mitigated some of the Board's concerns. Dr. Kim stated that randomization usually implies no overlap, but the protocol indicates overlap will occur; the investigator should plan for this properly.
Dr. Chambers remarked that because the protocol tests the three products independently and will not compare efficacies, overlap should have no effect. Dr. Kim added that the design dictates how to estimate error. If there is overlap, it may not be possible to estimate error. Dr. Chambers countered that only duration is of interest for labeling purposes, so error estimates are less consequential. Dr. Kim noted that when drawing statistical inferences, the mean alone is not sufficient. Standard error measurements are needed for the data to be valid.

Dr. Fisher inquired if pure randomization of 30 subjects (10 different subjects per condition) was sufficient to determine standard deviation. Dr. Kim replied that this was the decision of the investigator. Randomization of the 30 individuals is acceptable, as is a cross-over design, but this must be planned. Dr. Fisher questioned if the Board could recommend using 30 different subjects and not pooling the results. The Board should be consistent concerning the unacceptability of providing a mean without a standard deviation. Dr. Kim indicated that the investigator should provide an experimental design sufficient to allow interpretation of data.
Dr. Lebowitz said that the HSRB should provide EPA with guidance on information that should be included in submitted protocols. EPA will decide if investigators should be told that there is a risk of their data being objected if it is not performed in accordance with the revised protocol.

Dr. Fisher asked if the Board considered this protocol to also be premature for Board review and if the Board should inform EPA of what is needed to make the protocol acceptable for review (i.e., explicit randomization, sufficient numbers of subjects to allow calculation of standard deviation). Mr. Carley suggested that the Board avoid the term "premature" if it means that EPA and the Board wish to review the protocol before it is executed. Dr. Leibowitz said he would like some type of confidence from EPA that they belief the investigator will provide the information necessary to evaluate the completed study. Dr. Fisher summarized that the Board was not dictating whether a repeated measure or between subjects design should be used, but that which ever design is used it is insufficient to provide standard deviations and an inappropriate statistical analysis and that if appropriate analyses were not conducted the Board would be unlikely to judge the completed study as acceptable. Mr. Sweeney said this was helpful.

Ethical Considerations – SPC-002

Dr. Philpott opened discussion of the ethics of SPC-002. Once the recommended changes made by Mr. Carley and Mr. Sweeney are incorporated into the protocol, it will meet the requirements of 40 CFR part 26, subparts K and L. The risks are minimal and justified by the expected benefits. The risks include reactions to the test materials, tick bites, and vector-borne illnesses. The active ingredient found in the test products is commercially available in similar concentrations. People with known allergies to the products will be excluded. Stopping rules and medical management plans are in place.

Tick bites are unlikely given the seeking and biting behavior of ticks. Baring concerns about RMSF, which can be transmitted across generations, the ticks are laboratory-raised and pathogen free. Dr. Philpott supported Mr. Carley's request for more information concerning RMSF transmission.

The protocol minimizes coercion, compensation is not inappropriately high, and children and pregnant or nursing women are excluded. Alternative subjects are included to protect confidentiality with regard to pregnancy testing. The age limit should be increased above 55 years of age for environmental justice reasons. The psychosocial risks associated with an unexpected positive pregnancy test should be noted. Drs. Sharp and Fish agreed with Dr. Philpott's assessment.

Follow-up from Previous Day's Discussion

Mr. Jordan had no further follow-up from the October 25, 2007 session.

EPA Review of ICR Protocol G0590607001A117 (A117)

Introduction

Mr. Carley provided background on Protocol ICR A117. This protocol was submitted on behalf of Avon Products, Inc., by toXcel on August 8, 2007, and proposes a laboratory study performed by Insect Control and Research, Inc. (ICR), of repellent efficacy against *Culex* mosquitoes of two registered repellent products containing 10 percent picaridin. EPA's Science and Ethics Review of September 24, 2007 was based on review of the August 8, 2007 submission and previously accepted labels. The August 8, 2007 submission fell short of the standard of completeness defined in 40 CFR §26.1125, but in ways which did not compromise EPA's review. Although refinement is still needed to address all the deficiencies noted in EPA's Science and Ethics Review, EPA believes this protocol will benefit from HSRB review. In the October 17, 2007 submission by toXcel, the investigators promised to revise the protocol and consent forms to address most EPA comments. ICR and Avon want to continue to use the 1 g/600 cm^2 standard dose and to use FCB as the endpoint, for consistency with the earlier field studies of these products.

This is a proposal for research involving intentional exposure of human subjects, with the intent to submit the resulting data to EPA under FIFRA. Applicable regulatory requirements are 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. EPA differs from ICR in interpretation of §26.1125 documentation standards. EPA does not consider protocol drafts, consent forms, application forms, MSDSs, etc. to be IRB "correspondence." Also, consent forms cannot satisfy §26.1125(a)(1)-(5) requirements for discussions of risk, risk minimization, benefits, alternatives, and risk-benefit balance.

The submission lacked acceptable discussions of the nature and magnitude of all expected benefits of the research, and to whom they would accrue (§26.1125(a)(3)), the balance

of risks and benefits of the proposed research (§26.1125(a)(5)), and an acceptable description of the circumstances and methods proposed for presenting information to potential human subjects for the purpose of obtaining their informed consent (§26.1125(d)).

Scientific Considerations

Mr. Sweeney provided EPA's scientific assessment of ICR A117. This study proposes a cage test of *Culex* mosquito repellency for two formulations of picaridin. The repellent samples are expected to provide 8 hours of personal protection from *Culex quinquefasciatus* mosquitoes, a WNV vector, in the laboratory. The objectives of the study are to determine the mean protection time from bites provided by the test substances under laboratory conditions to confirm the hypothesis that these products repel *C. quinquefasciatus* mosquitoes and to support proposed label claims for efficacy against "mosquitoes which can vector West Nile virus."

Testing will be performed in a laboratory maintained at $80^{\circ} \pm 15^{\circ}$ Fahrenheit and 70 percent ±15-percent relative humidity. Six cages measuring 2x2x2 feet will be used. The cages are screened on the top and sides and mirrors are positioned on the bottom to allow monitoring of the underside of arms. There are 2 sleeved ports on each of opposite sides of the cage. There will be 2 subjects per cage who will participate in one 9-hour day of testing. The test mosquitoes will be female *C. quinquefasciatus* mosquitoes that are 3 to 8 days old, fasted, and have had no prior blood meal. Mosquitoes will be present at 100 per cage; 100 more per cage will be added if fewer than 5 landings per minute occur on the untreated control. These mosquitoes have been laboratory-colonized for many years and have had no exposure to outside blood sources. The mosquitoes also are destroyed after a single test. Because of these precautions, transmission of blood-borne disease is not possible.

All subjects must expose their untreated arms to the caged mosquitoes to establish attractiveness. The protocol calls for 10 treated subjects plus 2 treated alternates to ensure $N \geq 10$. Treated subjects will be treated with one formulation on each arm and will expose both arms to caged mosquitoes for 5 minutes at 30-minute intervals. One untreated subject, selected by lot, will monitor the aggressiveness of caged mosquitoes for 1 minute at 30-minute intervals.

The standard dose rate of 1 g product/600 cm^2, equivalent to 1.67 mg product/cm^2, will be used. One treatment will be applied to a 250 cm^2 area on each forearm of each treated subject. Each subject will receive a total dose (both arms) of 835 mg product (83.5 mg picaridin; 2.7 mg/kg for 70 kg adult). Based on the WHO-reported picaridin dermal NOAEL of 5,000 mg/kg, the MOE is ≥ approximately 1,800. Only subjects will be blinded. Measurements will be subject limb dimensions, time post-treatment of all bites on treated subjects, and landing rate on the untreated control's arm. The protocol has not proposed a form for recording results of attractiveness tests. Duration of efficacy will be measured as time from treatment to "FCB" or 8 hours, whichever occurs first. The protocol states that "ICR prefers to evaluate repellency based on protection from bites rather than landings while conducting laboratory studies." Mr. Sweeney explained that only a small area of skin is exposed in a cage-testing experiment and that mosquitoes will land up to the edge of the treated area. Repellent vapors do not affect landing in a cage-testing situation.

Analysis will employ nonparametric statistics, Cochran Q Test, cross-tabulations and Fischer's Exact Test. The mean time to FCB, with standard deviation and 95 percent confidence interval, will be reported if a normal distribution is observed. The median time to FCB and confidence interval by percentile will be reported if the distribution is significantly skewed. The untreated control will not be used for comparison and results will not be compared between the two formulations. A method for handling data from subjects who withdraw early was not specified. Regarding rationale for sample size, EPA guidelines recommend 6 replicates. An analysis by Rutledge and Gupta (1999) shows that a sample of 10 to 11 is needed to achieve with 95 percent confidence a standard deviation not greater than 2 hours after 8 hours of testing and ICR has stated that "This study, therefore, will use ten treated test subjects." Two additional alternate subjects will be treated, and will "help to ensure a minimum 'N' of 10 and will aid in protecting the privacy of any dropouts."

EPA has noted some deficiencies in this protocol. EPA guidelines call for 200 mosquitoes per cage; the proposed use of 100 per cage is not explained or justified. The explanation of diagnostic testing for normality of distribution and of analysis of non-normal data is incomplete. EPA also recommended that EPA-approved product labels be appended to the protocol. If the noted deficiencies are corrected, this protocol is likely to yield scientifically reliable information, satisfying the HSRB criteria that the research produce important information that cannot be obtained except by research with human subjects, has a clear scientific objective, and that the study design should produce adequate data to achieve the objective.

Dr. Chambers requested clarification concerning possible interference from repellent vapors, given the proximity of subjects' arms in the cage. Mr. Sweeney explained that such interference will not occur, particularly if 200 mosquitoes are placed in each cage.
Dr. Fitzpatrick inquired if all subjects will reach 8 hours without receiving a bite. Mr. Sweeney replied that if no bite occurs, the assumption will be that the product lasts for 8 hours. These products already have been tested and a protection time of 8 hours is supported. This protocol specifically tests repellency against *Culex*. Dr. Chambers questioned if comparable laboratory studies have been performed to test these products against other species of mosquitoes.
Mr. Sweeney responded that only field studies have been performed against other species.
Dr. Chadwick noted that the age of these mosquitoes was younger than the optimal age recommended by Dr. Gupta. Mr. Sweeney added that 3-day old mosquitoes are typically used in laboratory studies. Mosquitoes are ready for a blood meal within the first 2 days of life and become highly voracious within the first 10 days of life. Mosquitoes fasted from blood for a week would be less healthy.

Dr. Chadwick questioned why ICR prefers to use bites rather than landings to confirm product failure. Mr. Sweeney explained that biting is a more clear endpoint, but landing provides a more conservative measure. In a cage test with hundreds of mosquitoes in a cage, a landing might not be noticed. Dr. Lehman-Mckeeman asked Mr. Sweeney to explain the utility of the untreated control. Mr. Sweeney explained that the subjects will place an untreated arm in the cage once to test attraction and then repellent will be applied. This is to ensure that the mosquitoes are continuously feeding; however, if mosquitoes are observed to land on the subjects, it may not be necessary to include the other untreated controls. Mr. Carley clarified

that treated subjects are exposed before treatment to establish attraction and other untreated subjects are used to monitor biting pressure; if the designated threshold is not reached, more mosquitoes can be added to the cage. Mr. Sweeney added that, unlike some other repellents, picaridin does not appear to affect mosquito behavior.

Dr. Kim requested clarification on exposure times. Mr. Sweeney explained that subjects would be exposed for 8 hours. The statements concerning the 9-hour test day refer to the time the subjects will spend at the laboratory. Dr. Sharp inquired if subjects could take breaks. Mr. Carley explained that the subjects would have their arms in the cages for only 5 minutes per 30-minute time interval. Cyclic intermittent exposure will be used, not 8 hours of continuous exposure. Dr. Chambers asked how data from the 2 alternate subjects, added in case of drop-outs, would be used if none of the subjects drop out. Mr. Sweeney answered that this was unclear.

Dr. Philpott stated that he could not find a statement concerning exposure of untreated skin by treated subjects in the consent documents. Dr. Fisher commented that the consultants had indicated that continuous exposure was preferable to intermittent exposure and bites were more informative than landings. She noted that Avon has already performed field testing of this product and asked how the results of this study would be used. Mr. Sweeney explained that the results would determine whether this product also repels *Culex* mosquitoes. Mr. Carley explained that the use of intermittent exposure, a 250 cm^2 treatment area, and use of bites as an endpoint paralleled prior field tests. *Culex* mosquitoes were not present at the field testing site, therefore, laboratory testing of *Culex* repellency was needed. Dr. Fisher stated that given that this experiment is designed to test repellency against pathogen-carrying mosquitoes, that the Army uses continuous testing, and that continuous testing is preferable to intermittent exposure, she inquired whether it was important to perform the laboratory study using test conditions identical to the field testing. Mr. Carley commented that this was an open question. The proponent argues that parallelism is appropriate when trying to extend the range of regulatory inferences that can be drawn. Additionally, the research performed by the military is for public health rather than regulatory purposes; it is expected that the military will use a different approach.

Ethical Considerations

Mr. Carley presented EPA's ethical assessment of ICR A117. The proposed study would test the repellent efficacy of two registered products against *Culex* mosquitoes under laboratory conditions. Previous field tests showed efficacy against other genera, but *Culex* species were not present. EPA requires *Culex*-specific testing to support proposed label claims of efficacy against "mosquitoes which can vector West Nile virus." There is potential societal benefit in identifying repellents effective against potential vectors of WNV without exposing subjects to wild mosquitoes.

Subjects will be recruited among previous subjects of similar ICR tests and their friends and colleagues. The subject pool is characterized as being "as representative of potential repellent users as we are able to make it." Exclusion factors are anyone under 18 or over 55 years of age, pregnant or nursing women, those sensitive to repellents or to mosquito bites,

those in poor health or physical condition, those unable to speak and understand English, members of populations vulnerable to coercion or undue influence, and ICR employees or relatives of ICR employees, the sponsor, or any other interested party.

Eligibility criteria were inappropriately defined by including study requirements, such as abstaining from tobacco and alcohol use for 12 hours before the study, abstaining from use of scented products before and during the study, and wearing specified protective clothing during the study, including heavy socks and blue jeans. These are not eligibility criteria that can be applied *a priori* but instead are behavior rules that can be used to exclude a subject. Violation of these requirements on the day of testing may be grounds for removing a subject, but these criteria cannot be applied before the fact to determine eligibility. Changing the verbiage in the protocol to indicate that subjects must agree to adhere to the listed conditions would permit these to be defined as eligibility criteria.

ICR will protect the untreated part of subjects' forearms with bandages, and hands with gloves. The protocol calls for subjects to provide "their own blue jeans, heavy socks, and long-sleeved shirts." The consent form promises, but does not provide an explanation of "proper protective clothing." Blue jeans and heavy socks are not needed for a cage test in the laboratory; ICR requires this clothing to protect against mosquitoes that may escape from the cage. ICR also has technicians monitoring the area to capture escaped mosquitoes.

The product 806-29 is registered with Toxicity Category III "Caution" labeling. The product 806-31 is registered with Toxicity Category II "Warning" labeling based on eye irritation. The protocol includes a misleading reference to Toxicity Category IV for inhalation and skin irritation effects of picaridin. This is misleading because the highest toxicity category is used to label repellents. The consent form addresses hazards only of picaridin—not of the test products—and characterizes it as of "mild toxicity" for eye irritation and of "low toxicity" for other effects. The protocol and consent form must be revised to accurately characterize the hazard level of the test products. Risks of allergic or irritation responses from test materials are minimized by excluding sensitive candidates, limiting the area treated, and monitoring subjects closely.

Reaction to probes or bites, ranging from redness, swelling, and itching to anaphylaxis is another risk faced by subjects. This risk is reduced by excluding candidates sensitive to mosquito bites, encouraging untreated control subjects to shake off landing mosquitoes before they can bite, exposing untreated controls only long enough to confirm continued mosquito landing pressure, exposing only a small area of treated skin intermittently, and pairing subjects to watch each other for landing mosquitoes. This risk could be further reduced by treating landings as evidence of efficacy breakdown. EPA also questions encouraging untreated controls to shake off mosquitoes, because this would make it difficult to count landings. The mosquitoes used in testing are pathogen-free and have been laboratory-reared for many years. The mosquitoes will not have received a previous blood meal and will be destroyed after a single use. The risk of disease is characterized in the protocol variously as "zero" or as "minimal." The subject age is unnecessarily limited to younger than 55 years; this is not necessary when testing involves pathogen-free mosquitoes.

There are no direct benefits to subjects; the primary beneficiary is the sponsor. The societal benefit discussed in the protocol is of bringing new repellents to market; this is irrelevant in this case because the product is already commercially available. There is potential societal benefit in identifying repellents effective against vector species without exposing subjects to potential disease vectored by wild mosquitoes. Opportunities remain to further reduce risk while maintaining scientific robustness. If minimized, residual risks to subjects would be very low and the test materials are likely to prove effective and remaining risks to subjects are likely to be reasonable in light of potential societal benefits of identifying efficacy against *Culex* mosquitoes without exposing subjects to potential disease vectored by wild mosquitoes.

EPA also has considered risks to the control subjects who will establish biting pressure by placing an untreated arm in the cage at the beginning of each exposure cycle. These subjects are encouraged to shake off the mosquitoes to minimize bites. An alternative to this would be to consider the approach used by Carroll-Loye Biological Research and teach the subjects to aspirate landing mosquitoes. It is unclear if this is practical, but it would not be less effective than shaking for minimizing bites.

On July 30, 2007, the Essex Institutional Review Board, Inc. (EIRB) of Lebanon, NJ reviewed and conditionally approved the protocol and consent forms, subject to revision. The approved amendments 1-8 and revised consent forms were reviewed on August 7, 2007. The EIRB is independent of the sponsors and investigators, registered with the OHRP, but not accredited by the AAHRPP or the Partnership for Human Research Protection, Inc. (PHRP). EIRB was accredited by PHRP, but PHRP no longer accredits IRBs. EIRB is in the process of obtaining accreditation from AAHRPP, but progress toward accreditation is not reported by AAHRPP. EIRB procedures have been submitted directly to EPA under a Confidential Business Information (CBI) claim; EPA has reviewed them and determined they meet regulatory standards.

The inconsistent and vague descriptions of the recruiting and consent processes in the protocol and consent forms require clarification and reconciliation. Also, greater care is needed to impute no commitment to candidates before they have signed the consent form. The consent form must be revised to accurately characterize the hazards of the test products and to address risk of disease. The methods proposed for managing information about prospective and enrolled subjects will generally protect their privacy, if an inappropriate provision for subject signature on the control data collection form is revised. Subjects will be free to withdraw at any time and medical care for research-related injuries will be provided at no cost to the 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 this research are 40 CFR part 26, subparts K and L. A point-by-point evaluation of how the protocol as submitted addresses applicable standards appears as Attachment 1 to the EPA Science and Ethics Review. ICR has claimed that it has complied with EPA regulations by submission of documents and paperwork to EIRB; however, more is needed to achieve compliance.

EPA has noted some deficiencies in its review. The irrelevant discussions of societal benefits of new repellent products should be replaced by a discussion of the likely benefits of

adding new claims to registered labels, and to whom they would accrue. A discussion of the relation of risks and benefits of the research is needed. Risks from mosquito bites could be further reduced by treating landings and probes as evidence of efficacy failure; testing to FCB, which both increases subject risk and lowers the standard of efficacy, must be justified by more than ICR's stated preference. The inconsistent and incomplete descriptions of the processes of recruiting and informing the candidates and seeking their consent must be clarified and reconciled. The investigators must impute no commitment by a candidate to participate in the study before the consent form is signed. The provision for subject signature on the control data collection form should be deleted.

With EIRB approval of the requested revisions, all requirements of §26.1111, §26.1116, and §26.1117 would be met. With requested additional material, all requirements of §26.1125 would be met. The requirements of §26.1203 have been met. If revised as requested, protocol ICR A117 and the associated consent form will likely meet the applicable requirements of 40 CFR part 26, subpart K and L.

The Board is asked to address whether the proposed research described in ICR's proposed picaridin protocol, if revised as suggested in EPA's review, appears likely to generate scientifically reliable data, useful for assessing the efficacy of the test substances for repelling mosquitoes of the genus *Culex* and whether the research appears to meet the applicable requirements of 40 CFR part 26, subparts K and L.

Dr. Fitzpatrick questioned whether EPA would permit bites to be used as evidence of efficacy failure. Mr. Carley responded that this is permitted under existing guidelines, although these guidelines may be revised. Currently, the guidelines do not mention using landings. EPA will accept a study that uses bites, but the protocol should justify why this standard for efficacy failure was chosen. Dr. Krishnan asked Mr. Carley to clarify the toxicity hazard of the products. Mr. Carley explained that the highest hazard is eye irritation. Because repellents will be applied to the arm by a technician, the risk of eye irritation is minimal. Subjects could accidentally touch their arms and deliver product to their eyes and thus must be informed of this potential hazard. Eye irritation is not appropriate for calculating MOE, which is why dermal MOE was calculated for this protocol.

Public Comments

Dr. Niketas Spero, on behalf of ICR, Inc. and Dr. Robin Todd, on behalf of ICR, Inc.

Dr. Niketas Spero (ICR, Inc.) clarified the use of bites as an endpoint for the A117 protocol. ICR conducted field studies to justify registration of these products. At EPA's request, ICR is conducting this laboratory study to determine efficacy against *Culex* mosquitoes. To adhere to the same parameters as used in the field studies, the same application rate and endpoint (bites) were used. Concerning the control subjects, the goal is for these subjects to receive no bites. The criterion used to verify landing rate in the cages is 5 landings within 60 seconds. These mosquitoes are very aggressive and the landings should occur quickly. A technician will verify the landings and the subject will then immediately remove his or her arm. Use of an

aspirator to collect landing bugs would complicate and confound this process. In the experience of ICR, control subjects usually receive no bites.

Regarding the justification for the statistical analyses, if the data are normal (as determined by a Z test for normality), the mean time of protection with 95 percent confidence interval and standard deviation will be presented. If the data are non-normal with a negative skewness, the data will be reflected using a log transformation, and the median protection time and upper confidence interval will be determined. Each subject will have 16 observations and these events will be plotted over each half hour to show regression of protection time.

Dr. Fisher asked Dr. Spero to clarify ICR's decision to use bites instead of landings to test efficacy; EPA has suggested changing this. Dr. Fisher also asked Dr. Spero to explain ICR's response to deficiencies noted by EPA and whether and how ICR intended to address these deficiencies. Dr. Spero answered that ICR fully intends to address the deficiencies and unclear or conflicting items in the protocol. ICR's intended actions were not fully described in the response letter because of time constraints. Dr. Fisher suggested that, in the future, the details of a sponsor's intended changes be included in the response letter for HSRB evaluation. The letter could state that the sponsor has not had time to revise the protocol to address the deficiencies, but fully intends to do so.

Dr. Kim addressed ICR's use of the Q test and asked for clarification of how loss of efficacy would be determined. Dr. Spero explained that once a subject received two bites, the subject would withdraw from testing. Dr. Kim stated that if a subject drops out, the Q test is invalid. Dr. Robin Todd (ICR, Inc.) explained that a statistician at Loyola University in Baltimore, MD has agreed to perform the statistical analyses and that he and Dr. Spero were unable to answer Dr. Kim's question. Dr. Kim inquired how data would be analyzed if a subject did not receive a bite within 8 hours of exposure. Dr. Spero indicated that if no bite is received, a protection time of 8 hours will be assumed. Dr. Kim noted that normal analyses are inappropriate if this assumption is made.

Dr. Philpott commented that the protocol indicated that subjects would shake their arms to remove landing mosquitoes but the informed consent form indicates that subjects will brush the mosquitoes away and asked for clarification. Dr. Spero explained that the informed consent form was incorrect and that the statement regarding brushing mosquitoes away would be removed. Dr. Lehman-Mckeeman noted that ICR's rationale for using bites was to maintain consistency with the field testing; however, given that *Culex* mosquitoes were not present in the field, she asked how this comparison was valid. Dr. Spero answered that ICR wished to keep application rate and endpoints consistent between the field and laboratory studies. Dr. Lehman-Mckeeman inquired why the repellents would be applied using a syringe because this is not how repellents are usually used. Dr. Spero explained that this was to allow application of a known amount of repellent. Dr. Fisher questioned whether repellent vehicle was a factor in using this application process. Dr. Spero stated that the goal of this procedure was to apply a known amount to a known area.

Dr. Sharp asked Drs. Spero and Todd to comment on possible stress to subjects due to remaining in a warm, humid environment and having to keep their arms in the mosquito cage.

Dr. Spero replied that they have never had people faint or become light-headed during the test process. Subjects are allowed to take breaks, and the major complaints have been boredom, tedium, and the humidity. Dr. Chambers inquired if the mosquitoes show consistent biting pressure between batches. Dr. Spero responded that the mosquitoes are essentially sisters and do show consistent biting pressure.

Dr. Fisher returned to the issue of application procedure. Because the tested products are spray formulations, she asked how application of a known amount using a syringe was relevant to consumer use. She asked if ICR had performed dosimetry to estimate consumer use and dose. Dr. Spero explained that ICR had not performed dosimetry but had used EPA guidelines and recommended application rates. ICR wishes to dispense and apply a known amount of product to a known area for consistency and to parallel the field study. Dr. Fisher questioned whether dosimetry would be of value. Dr. Spero replied that dosimetry may be of value in the future, but it is unclear whether it would be of value for this study. He indicated that ICR will consider adding dosimetry.

Dr. Fisher made the general point that in the future, either the statistician working with the sponsor should be present at the HSRB meeting or should be consulted prior to submission of the protocol. The Board wishes to prevent situations in which a study is conducted but the analysis is found to be inappropriate or insufficiently powered after completion. The Board needs more direct information from the statistician and a more explicit statistical plan.

Dr. Lebowitz stated that, given tight schedules, sponsors or agents may not have sufficient time to provide EPA and the HSRB with their response to deficiencies noted by EPA. He asked Mr. Carley to explain the timeline of EPA's submission of comments to ICR and receipt of ICR's response. Mr. Carley explained that ICR received EPA comments within 24 hours of completion of EPA's review of the protocol; ICR received EPA's review on September 25, 2007.

Dr. Kim expressed frustration with the statistical deficiencies in the protocols submitted for HSRB review. To adequately address the scientific soundness of a protocol, more information on statistical analysis plans is needed and the HSRB also should have the opportunity to question the statistician working on the protocol.

Dr. Fisher stated that although the Board understands that many of these studies can be performed only during a short time of the year, the Board should only rarely review a protocol to which the sponsor has not had time to respond. This should be particularly rare for a laboratory study, because these studies can be performed at any time of the year. The deficiencies of this protocol should have been addressed and a statistical analysis plan provided. She indicated that she did not want the Board to reject studies because of inadequate information, but did want sponsors to understand the type of information the Board needs to adequately review the protocols. In the future, she requested that the Board not be asked to review protocols for which there are no statistical analysis plans. Dr. Lebowitz agreed and added that the HSRB should receive this information at least one week prior to the HSRB meeting during which the protocol will be discussed.

Board Discussion

Scientific Considerations – ICR A117

Dr. Chambers opened the science discussion of ICR A117. This is a hypothesis-based study to determine if the products provide 8 hours of protection against *Culex* mosquitoes. The protocol was clearly written. The number of insects per cage will be increased to 200, which is adequate. The rationale for dosage and dosimetry using standard EPA guidelines and approaches used in a previous field study is acceptable. This study compares registered products to establish a claim for other species and so should parallel the previous field study. Dr. Chambers indicated that she was unsure whether dosimetry would be of value to this study, but EPA may wish to consider adding this to its guidelines. Because bites were used in the previous study to indicate efficacy failure, it is appropriate to use bites in this study to expand label information. The mosquitoes are pathogen-free and thus do not present a danger to subjects. Potential subjects are told in the informed consent form that they will receive bites, but the number of bites will be limited. The use of bites as an endpoint and the dosing and application methods are appropriate to maintain consistency with the field study.

Dr. Lehman-Mckeeman stated that she disagreed, but not strongly, with Dr. Chamber's opinion regarding dosimetry. The study purpose is to support a claim of protection against *Culex*. It is unclear how this study is directly comparable to the field study because *Culex* mosquitoes were not present in the field. If the claim is to be specific against WNV, which is a serious disease, the notion that there needs to be direct comparison to the field study is not persuasive. This study should be considered a stand-alone study; the study is performed for appropriate reasons, so following EPA guidelines is acceptable. If the goal is to develop a claim against *Culex*, the study will generate meaningful data, but it does not need to be directly comparable to the field study.

Dr. Fitzpatrick remarked that although the sponsors are the primary beneficiary, this study will benefit consumers by providing a product that protects against *Culex* mosquitoes. A dosimetry phase is not needed; use of EPA guidelines is sufficient for this study. Intermittent exposure is appropriate, and much more feasible than continuous exposure in this setting. Using bites as an endpoint is acceptable if subjects understand that they will receive bites. She noted that in general, when a regulatory agency describes deficiencies to a sponsor, the sponsor will address the deficiencies, particularly if they are easily addressed. Dr. Fisher added that EPA must articulate its faith that the sponsor will address the deficiencies.

Dr. Parkin agreed with Dr. Chamber's assessment. Dr. Chambers added that, to defend the sponsor's claims for a need for consistency, the labels on the products will remain the same, except for wording added to indicate efficacy against *Culex* mosquitoes. If the label will not be changed in any other way, the dose and endpoints need to be the same. Dr. Lebowitz inquired if other mosquito species that carry WNV were present during the field study. He also noted that to match the field study, the temperature and relative humidity in the laboratory should be the same as that of the field site. He asked whether the laboratory conditions mimic weather conditions in which WNV carriers are active. He concluded that the laboratory study likely will not mimic the field study sufficiently and also does not test other types of mosquitoes that carry

WNV. Since the goal of the study is to change the label to indicate protection against WNV, these issues are of concern.

Dr. Kim inquired if the hypothesis that the samples will provide 8 hours of protection meant an average of 8 hours. He asked how this would be verified if the observation period would be only up to 8 hours. He stated that it was unclear whether this study could provide this data. Occurrence of an event before 8 hours indicates failure. The sample size was justified based on standard deviation around 8 hours of protection; this information cannot be obtained if the observation period is limited to 9 hours. The analysis plan also ignores censoring and the sample size calculation is incorrect. Dr. Fisher indicated that alternate subjects would be present to account for censoring; only data from subjects completing the exposure period would be included. Dr. Kim stated that data from subjects who withdraw early should not be removed from the dataset. In addition, he explained that if a bite is not observed after 8 hours of exposure, this is a censored observation, which is not the same as dropping the data point.

Mr. Sweeney explained that the temperature and relative humidity in the laboratory were similar to the conditions of the field testing, which was performed in Georgia and Florida. A variety of genera were present at the field sites, and repellency against these genera was established. EPA requires a sponsor to establish protection only against one genera to support protection claims. *Culex quinquefasciatus* or *Culex tarsalis* are the principal vectors used for testing; *Culex quinquefasciatus* are easier to raise in the laboratory. These two *Culex* species are the primary WNV vectors in the United States.

Regarding the statistical analysis and why testing would last only 8 hours, this time period was chosen based on 100-percent protection at 8 hours, which is the sponsor's choice. Regarding censoring of data and whether a correct mean can be determined, Mr. Sweeney agreed with the Board's concerns; the test period might need to be increased. He was unclear whether issues of variability and use of proportions would affect the Q test. Dr. Kim indicated that the Q test is a secondary supportive analysis. The primary concern is that if the endpoint is time to efficacy failure and efficacy does not fail before 8 hours, the study fails to establish the protection claim. Dr. Fisher inquired if the sponsor's claim of 8 hours of efficacy was incorrect if a bite was observed within 8 hours. Dr. Kim responded that only a claim of less than 8 hours could be made. Dr. Lebowitz suggested that the label could indicate up to 8 hours of protection. Dr. Fisher questioned if there would be a way to interpret the data if a subject received a single bite in less than 8 hours. Mr. Sweeney replied that any bite received by a subject will be recorded. If a subject leaves the study before receiving a confirming bite, the first bite will be included. Dr. Fisher asked if the label would claim that the product is protective against some species that carry WNV. Mr. Sweeney explained that the label would indicate that the product repels mosquitoes that may transmit WNV, but would not specify which mosquitoes.

Dr. Johnson noted that the tests proposed in the protocol are not the same as those described during the Public Comments session. Dr. Fisher stated that the test of binomial proportion was not powerful for small sample sizes. The Kaplan-Meier analysis provides sound information and may be able to help with censoring. Mr. Sweeney commented that at the beginning of the HSRB review process, a recurring deficiency has been lack of detailed explanations concerning how to analyze the data. Researchers may propose one form of analysis

and then may wish to change it after the data are gathered, but the study design should match the proposed analysis. Dr. Kim stated that deciding on analysis after gathering the data leads to bias; analysis needs to be planned before conducting the experiment. Dr. Fisher remarked that the Board does not want to review protocols unless an analytic plan is presented. She concluded that some details need to be clarified for ICR A117, the issues raised in discussion are not limitations, and the study is likely to generate scientifically reliable data.

Ethical Considerations – ICR A117

Dr. Philpott opened the ethics discussion of ICR A117. He agreed with Mr. Carley's observations concerning the strengths and weaknesses of the protocol. Once the recommended changes are made, the research will meet the applicable parts of 40 CFR part 26, subparts K and L. Concerning the issue of bites versus landings, because the protocol uses pathogen-free mosquitoes, this is not a significant issue. The risks to participants are minimal and justified by the benefits. The risks are reaction to the product, bites, and exposure to vector-borne disease. The active ingredient in the products is commercially available as are the products themselves. Dr. Philpott agreed with Mr. Carley's comments regarding correction of the mischaracterization of toxicity risk. Because the products are already marketed, people with allergies can be excluded. Only a limited amount of skin is exposed to biting mosquitoes and adverse events are unlikely. Clear stopping rules and a medical plan are in place.

The endpoints require two confirmed bites to document product breakdown. There is a risk of bites to control subjects, but reactions to mosquito bites are mild and easily treated. Exclusion of people with severe reactions to mosquito bites minimizes risk. The mosquitoes are laboratory-raised and pathogen-free, so risk of disease is minimal. This information may not need to be included in a risk category, but could be included in the informed consent form to alleviate subjects' concerns. There is no justification for exclusion of people older than 55 years of age, but this may have been left over from the field study. A more detailed explanation of subject recruitment is needed, but as written, compensation is not coercive; employees, contractors, and family members of the sponsor are appropriately excluded; and children and pregnant or nursing women also are excluded. Alternate subjects are included to protect confidentiality related to the results of pregnancy testing.

Dr. Philpott described some minor corrections. Regarding the differential risks to untreated controls, the informed consent form should be corrected to indicate that controls will shake off mosquitoes rather than brush them off. The informed consent form also needs to explain the "attractiveness" test (placement of an untreated arm in the cage to ensure attractiveness to mosquitoes) that subjects will perform before beginning the efficacy study. The statement regarding the benefit of adding a new repellent to the market also must be corrected in the informed consent form.

Dr. Chadwick agreed with Mr. Carley's and Dr. Philpott's assessment. He stated that he was comfortable with ICR's rationale for using bites instead of landings. There is minimal risk to the subjects, and this risk is ethically acceptable. The informed consent form must correctly address the purpose of the research and correct the risk categorization. There also is no reason to exclude those over 55 years of age because risk of contracting WNV is minimal.

Dr. Sharp noted that the primary risk to subjects was remaining in a hot, humid environment for long periods of time. The language of the protocol is ambiguous with respect to this risk, and merely indicates that eligible subjects must be able to withstand the rigors of testing; exclusion of those over 55 years of age may have been intended to minimize this risk. The medical monitoring plan needs to be described in more detail, including a plan to cope with rare events such as a subject's loss of consciousness. The request for pre-enrollment behavior changes regarding clothing and hygiene are not problematic or atypical.

Dr. Fisher summarized that although changes need to be made in the protocol and informed consent forms, EPA and the HSRB are confident these changes will be made. Regarding exclusion of those over 55 years of age, the Board had mixed opinions about this with respect to comparability between the laboratory and field studies. There is no harm in maintaining 55 years as a ceiling and no evidence for difference in efficacy related to age, so the results will be generalizable. The attractiveness test must be added to the informed consent form and the purpose of the study corrected to indicate that the study is not testing a new product. The risks of heat and other minor risks associated with the test environment should be included on the informed consent form. The absence of WNV risk should be explained more clearly, as should the medical plan. The pre-enrollment behavior changes do not need to be included in the informed consent form. Potential subjects also should be given the chance and means to return home if they do not participate in the study.

Dr. Fisher reaffirmed that in the future the HSRB does not wish to review protocols that are unaccompanied by a plan for statistical analysis. In addition, when EPA has presented needed modifications to an applicant, the HSRB would like to see an indication that the changes will be made. Dr. Lewis clarified that the public is asked to submit comments within 7 days to permit public review; receipt of comments is acknowledged. Dr. Fisher stated that a letter indicating that the changes will be made but time constraints prevented this is acceptable. Such a letter should indicate the changes the applicant will comply with and also an explanation of why some changes may not be made.

Dr. Fisher explained that the HSRB had requested that the agenda for the next Board meeting include a period for consultation with statistical experts regarding design models. These consultants should be familiar with the constraints of studies reviewed by the Board and how such studies can be properly analyzed. Repellent studies are generally characterized by small sample sizes, constraints on subjects' activities, and other issues.

EPA Update of Antimicrobial Exposure Assessment Task Force (AEATF) and Agricultural Handlers Exposure Task Force (AHETF) Research Programs

Mr. Jordan presented a brief report of EPA progress on sampling strategy issues for the AEATF and AHETF discussed at a June 2007 Board meeting. EPA has worked with the task forces to address issues with the sampling strategies that were raised by the HSRB. At the June 2007 HSRB meeting, EPA asked the Board to review documents related to the research proposed by AHETF and AEATF. The purpose of the task force research is to generate data on exposures received during specific tasks, including mixing, loading, and applying pesticides. At

the June 2007 meeting, the purposive diversity sampling (PDS) strategy planned by the task forces was described. The HSRB reviewed this approach unfavorably and concluded that statistically defensible inferences about exposure pertaining to the larger handler population could not be drawn if PDS was used. The Board recommended a random sampling strategy that drew from the target populations.

After the June 2007 meeting, EPA and the task forces discussed Board recommendations at length. The task forces have three primary concerns. First, the task forces continue to believe that PDS will provide reliable data because of the manner in which subjects will be selected, and the task forces trust in the expert selection of conditions to monitor. This approach will skew the data toward conditions associated with higher exposure. If exposure conditions are unclear, selection will occur across a range of factors, such as geographic location or based on loading practices. The task forces argue that the data will be relevant and EPA will be able to use the data to make inferences about exposure occurring in the larger handler populations.

Secondly, the task forces are concerned about issues of timing, particularly the AHETF. This research must be performed during 2008; thus the task forces need to know EPA's position on the research far enough in advance to plan protocols; submit the protocols for IRB, EPA, and HSRB review; adjust the protocols; and execute the protocols in the field during the appropriate time of year. Based on information provided by the task forces, EPA believes that the task forces must learn by early November 2007 whether PDS will be acceptable. EPA believes the data gathered from these studies will greatly improve existing data on exposure.

Lastly, the task forces are concerned about the feasibility and costs of acting on the HSRB's recommendation to use a random sampling strategy. The task forces claim that to use the HSRB's random sampling approach would require massive revision of sampling strategies and would be costly. At present, program changes the task forces have made in response to feedback from EPA and the HSRB has led to significantly increased projections of the cost of the research program; the task forces now are unsure if they can afford to perform this research. Because of cost issues, using a random sampling approach would require the task forces to abandon several of the scenarios. This would result in loss of some members of the task force, which would decrease available funding and further limit the amount of research that could be performed.

OPP has attempted to work on these issues with the task forces. To understand the scientific and financial implications of the changes, OPP has asked the Secretariat of the Scientific Advisory Panel [SAP] (which identifies experts to serve on SAPs and address specific issues) to help address the sampling issue. This has been challenging, largely because of timing issues. Dr. Takagrata Miti, an associate professor at Iowa State University and colleague of Dr. Carriquiry, has expertise in survey sampling and was asked to review documents, HSRB and SAP reports, and other information provided by the task forces. Dr. Miti met with OPP staff and some members of both task forces on October 17-18, 2007. Presentations were made concerning how PDS would be used and the associated cost and feasibility issues of concern to the task forces. Dr. Miti provided valuable independent assessments of these issues. The task forces could not provide a detailed cost breakdown of random sampling, which they believe

would require pilot experiments. Dr. Miti also could not provide an exact prediction of potential cost increases.

EPA has identified specific questions for Dr. Miti, which he will answer in a written report. EPA will subsequently review this report and decide how to move forward. The task forces must decide whether it is still feasible to plan these experiments for 2008 and require a decision from EPA by early November 2007 to do so. If the task forces decide to proceed with the research, they will attempt to have a protocol ready in January 2008. By this time, EPA will have made its decision and will be prepared to present an explanation for it. At the HSRB meeting in January 2008, the issues around sampling will be discussed before task force protocols are reviewed.

Board Discussion

Dr. Fisher explained that she had hoped to be able to discuss issues pertaining to PDS versus random sampling independent of a specific protocol. The Task Force Work Group had suggested inviting consultants to discuss this issue at the October 2007 Board meeting, but EPA rejected this idea because the Agency believed its own consultant would be ready to address the Board. Dr. Fisher stated that she was disappointed that this had not been possible. She hoped that the Board, EPA, and task forces would be in agreement with the November 2007 decision, but there will be no opportunity for feedback from the HSRB on this issue until January 2008. She indicated that the lack of certainty regarding the HSRB's response to this issue is a particular issue for the AHETF because of its need to submit a protocol in January 2008 to perform seasonal research. Mr. Jordan clarified that research on activities taking place in the Spring 2008 would need to be reviewed in January 2008; other activities that occur in the Summer 2008 could be reviewed at subsequent HSRB meetings.

Dr. Lebowitz suggested that a Board work group could review the deliberations made by EPA's statistician within the next month and provide this to the HSRB members. Dr. Fisher agreed that such a process could follow the CBI model; a work group would review the material to determine if it is adequate for HSRB review. The HSRB has statistical and agricultural experts who could contribute to this review. Dr. Lewis reminded Board members that any decision of such a work group could not be considered to be representative of HSRB decisions. Mr. Jordan stated that the materials received from the task forces at the October 17-18, 2007 meeting could be provided to Board members. A written report from Dr. Miti is expected in the near future, and also could be provided to the Board. EPA will discuss this material internally (likely to be oral rather than written) sometime between November 2007 and when preparations for the January 2008 meeting must take place. The outcome of this oral discussion will be used to generate written comments and perhaps also presentation materials.

Dr. Fisher stated that the tension between financial concerns and statistical matters regarding random sampling was a primary concern. She indicated that she understood that once a decision was made by EPA, the task forces will act on this decision and the Board will review the task forces' protocols in January 2008. She agreed that an HSRB work group that would review Dr. Miti's report and any other relevant material would be helpful. This exercise would also provide EPA with information concerning the HSRB's understanding of the situation. She

proposed that this potential work group include Drs. Richard Fenske, Carriquiry, Johnson, Kim, and Lebowitz. Dr. Fisher stated that she considered this to be a useful approach, particularly to avoid situations in which the HSRB cannot approve EPA's use of data because of statistical issues. It is preferable that Board concerns be raised during protocol development rather than after the fact. Earlier input to EPA and the task forces from Board experts will help streamline the review process and make it collaborative, rather than confrontational. Dr. Krishnan echoed and supported the proposal to develop a task force work group.

Dr. Brimijoin expressed pessimism over the outcome of these discussions; however, he considered any effort to rescue a major and important project to be warranted. He stated that he was pessimistic about the success of this project unless the statisticians develop a way to perform random sampling that does not increase costs. He feared that the task forces may be asked to use a strategy that would both delay progress and increase costs, such that the task forces would decide not to do the research. It could be catastrophic if the Board will not recommend use of data collected using PDS. Dr. Fisher agreed that EPA needs a new dataset for handler exposure, but the Board must ensure that the data are usable. The HSRB's goal is to identify potential weaknesses, which could be beneficial for planning purposes, not to be adversarial. Dr. Johnson said that once the Board reviews the reports from Dr. Miti, it can decide whether or not to convene the work group. Dr. Johnson also noted that he had disagreed with Dr. Carriquiry's opinion regarding use of PDS versus random sampling. Dr. Fisher added that the Board also could clarify that data gathered using PDS could be used for some purposes but not others. Dr. Lebowitz agreed with Dr. Johnson that the Board should review the reports before deciding on its next steps. Disagreement among statisticians can be acceptable and is not detrimental to the process for either the task forces or EPA. It also would allow progress toward ensuring the data are useful once they are collected.

Dr. Fisher clarified that it is not desirable for the research to proceed until the Board can recommend that the data will be useable for the stated intentions. Dr. Lebowitz noted that many of the observational studies performed by NERL do not use random sampling, and there is some degree of overlap between these and the handler exposure studies. NERL may be able to provide important information concerning sampling strategies. Dr. Fisher suggested that Drs. Fenske, Carriquiry, Johnson, Kim, and Lebowitz review the materials. A work group call will be held including these Board members and also Drs. Fisher, Brimijoin, and Lewis, and Mr. Jordan.

Dr. Lewis thanked Dr. Fisher for serving as chair of this meeting. He also thanked Board members for their efforts and his EPA colleagues for their preparation and presentations given at this meeting. He stated that a *Federal Register* notice will be placed to inform the public about the availability of the Board's report for this meeting. Dr. Lewis also stated that review of the June 2007 report would be conducted by teleconference on November 13, 2007, and that a *Federal Register* notice would be placed to inform the public of this event. The next public meeting will be held January 15-18, 2008, and also will be announced in the *Federal Register*.

Dr. Fisher adjourned the meeting.

Respectfully submitted:

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

Certified to be true by:

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

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

Attachments

Attachment A	List of HSRB Members and Attending Consultants
Attachment B	Federal Register Notice Announcing Meeting
Attachment C	Meeting Agenda
Attachment D	Discussion Questions for Mosquito Repellent Studies

Attachment A

EPA HUMAN STUDIES REVIEW BOARD MEMBERS

Chair

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

Vice Chair

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

Members

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

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

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

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

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

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

Dallas E. Johnson, Ph.D.
Professor Emeritus
Department of Statistics
Kansas State University

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

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

Michael D. Lebowitz, Ph.D., FCCP
Professor Emeritus of Medicine
University of Arizona

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

Jerry A. Menikoff, M.D.
National Institute of Health
Office of Human Subjects Research

Rebecca Parkin Ph.D., MPH
Associate Dean for Research and Public Health Practice
School of Public Health and Health Services
The George Washington University

Sean Philpott, Ph.D., M.Bioethics
Policy and Ethics Director
Global Campaign for Microbicides
Program for Appropriate Technology in Health

Ernest D. Prentice, Ph.D. *
Associate Vice Chancellor for Academic Affairs
Professor of Genetics, Cell Biology and Anatomy
Professor of Preventive and Societal Medicine
University of Nebraska Medical Center

Richard R. Sharp, Ph.D.
Director of Bioethics Research
Department of Bioethics
Cleveland Clinic

Consultants

Germaine Buck Louis, Ph.D.
Division of Epidemiology, Statistics & Prevention Research
National Institute of Children & Human Development

P. Barry Ryan, Ph.D.
Department of Environmental and Occupational Health
Rollins School of Public Health
Emory University

Col. Raj. Gupta, Ph.D.
Director, Research Plans and Programs
Walter Reed Army Medical Center
Medical Research and Material Command

Steve Schofield, Ph.D.
Communicable Disease Control Program
Force Health Protection
Canadian Forces Health Services Group — HQ Ottawa
Department of National Defence

Daniel Strickman, Ph.D.
National Program Leader
Program 104: Veterinary, Medical, and Urban Entomology
USDA, ARS

* Not in attendance

Attachment B
Federal Register Notice Announcing Meeting

Human Studies Review Board; Notice of Public Meeting

[Federal Register: September 27, 2007 (Volume 72, Number 187)]
[Notices]
[Page 54908-54910]
From the Federal Register Online via GPO Access [wais.access.gpo.gov]
[DOCID:fr27se07-50]

ENVIRONMENTAL PROTECTION AGENCY
[EPA-HQ-ORD-2007-0942; FRL-8474-4]

Human Studies Review Board; Notice of Public Meeting

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

SUMMARY: The U.S. Environmental Protection Agency's (EPA or Agency) Office of the Science Advisor (OSA) announces a public meeting of the Human Studies Review Board (HSRB) to advise the Agency on EPA's scientific and ethical reviews of human subjects' research.

DATES: The public meeting will be held from October 24, 2007 from approximately 8:30 a.m. to approximately 3:30 p.m.; October 25, 2007 from approximately 8 a.m. to approximately 6:30 p.m.; and October 26, 2007 from approximately 8 a.m. to approximately 3 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 Crystal Rodgers-Jenkins, EPA, Office of the Science Advisor, (8105R), Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460; telephone number: (202) 564-5275; fax: (202) 564-2070; e-mail addresses: rodgers-jenkins.crystal@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-2007-0942, by one of the following methods:

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

E-mail: ord.docket@epa.gov.

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

Hand Delivery: The EPA/DC Public Reading Room is located in the EPA Headquarters Library, Room Number 3334 in the EPA West Building, located at 1301 Constitution Ave., NW, Washington, DC. The hours of operation are 8:30 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-2007-0942. EPA's policy is that all comments received will be included in the public docket without change and may be made available online at http://www.regulations.gov, including any personal information provided, unless the comment includes information claimed to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Do not submit information that you consider to be CBI or otherwise protected through http://www.regulations.gov or e-mail. The http://www.regulations.gov Web site is an "anonymous access" system, which means EPA will not know your identity or contact information unless you provide it in the body of your comment. If you send an e-mail comment directly to EPA, without going through http://www.regulations.gov, your e-mail address will be automatically captured and included as part of the comment that is placed in the public docket and made available on the Internet. If you submit an electronic comment, EPA recommends that you include your name and other contact information in the body of your comment and with any disk or CD-ROM you submit. If EPA cannot read your comment due to technical difficulties and cannot contact you for clarification, EPA may not be able to consider your comment. Electronic files should avoid the use of special characters, any form of encryption, and be free of any defects or viruses.

SUPPLEMENTARY INFORMATION:

I. Public Meeting

A. Does This Action Apply to Me?

This action is directed to the public in general. This action may, however, be of interest to persons who conduct or assess human studies, 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. 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 2007. In addition, the Agency may provide additional background documents as the materials become available. You may obtain electronic copies of these documents, and certain other related documents that might be available electronically, from the regulations.gov Web site and the EPA HSRB Web site at http://www.epa.gov/osa/hsrb/. For questions on document availability or if you do not have access to the Internet, consult the person listed under **FOR FURTHER INFORMATION**. Public comments received on the document titled, "Scientific and Ethical Approaches for Observational Exposure Studies," may be listed under Docket ID No. EPA-HQ-ORD-2007-0972 or Docket ID No. EPA-HQ-ORD-2007-0942.

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

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

a. Explain your views as clearly as possible.

b. Describe any assumptions that you used.

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

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

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

D. How May I Participate in This Meeting?

You may participate in this meeting by following the instructions in this section. To ensure proper receipt by EPA, it is imperative that you identify docket ID number EPA-HQ-ORD-2007-0942 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 17, 2007. To the extent that time permits, interested persons who have not pre-registered may be permitted by the Chair of the HSRB to present oral comments at the meeting. Each individual or group wishing to make brief oral comments to the HSRB is strongly advised to submit their request (preferably via email) to the person listed under **FOR FURTHER INFORMATION CONTACT** no later than noon, Eastern time, October 17, 2007 in order to be included on the meeting agenda and to provide sufficient time for the HSRB Chair and HSRB Designated Federal Officer (DFO) to review the agenda to provide an appropriate public comment period. The request should identify the name of the individual making the presentation, the organization (if any) the individual will represent, and any requirements for audiovisual equipment (e.g., overhead projector, LCD projector, chalkboard). Oral comments before the HSRB are limited to five minutes per individual or organization. Please note that this limit applies to the cumulative time used by all individuals appearing either as part of, or on behalf of an organization. While it is our intent to hear a full range of oral comments on the science and ethics issues under discussion, it is not our intent to permit organizations to expand these time limitations by having numerous individuals sign up separately to speak on their behalf. If additional time is available, there may be flexibility in time for public comments. Each speaker should bring 25 copies of his or her comments and presentation slides for distribution to the HSRB at the meeting.

b. Written comments. Although you may submit written comments at any time, for the HSRB to have the best opportunity to review and consider your comments as it deliberates on its report, you should submit your comments at least five business days prior to the beginning of the meeting. If you submit comments after this date, those comments will be provided to the Board members, but you should recognize that the Board members may not have adequate time to consider those comments prior to making a decision. Thus, if you plan to submit written comments, the Agency strongly encourages you to submit such comments no later than noon, Eastern Time, October 17, 2007. You should submit your

comments using the instructions in Unit I.C. of this notice. In addition, the Agency also requests that person(s) submitting comments directly to the docket also provide a copy of their comments to the person listed under **FOR FURTHER INFORMATION CONTACT**. There is no limit on the length of written comments for consideration by the HSRB.

E. Background

A. Topics for Discussion

The HSRB is a Federal advisory committee operating in accordance with the Federal Advisory Committee Act (FACA) 5 U.S.C. App.29. 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.

The October 24-26, 2007 meeting of the Human Studies Review Board will address scientific and ethical issues surrounding:

- Review of EPA draft document *Scientific and Ethical Approaches for Observational Exposure Studies*. The document, prepared by researchers in EPA's National Exposure Research Laboratory, identifies the types of issues that should be considered in planning and implementing observational human exposure studies and provides information and resources to assist EPA researchers in these studies.
- A published report of a completed clinical trial measuring the effects of single and repeated treatments with sodium azide on blood pressure in human subjects. Sodium azide is a pesticidally active ingredient being proposed as a replacement for the fumigant methyl bromide.
- A research proposal from Carroll-Loye Biological Research to evaluate the field efficacy in repelling mosquitoes of three registered products containing picaridin.
- A research proposal from Carroll-Loye Biological Research to evaluate the laboratory efficacy in repelling ticks of three registered products containing picaridin.
- A research proposal from Insect Control & Research, Inc. to evaluate the laboratory efficacy in repelling mosquitoes of the genus *Culex* of two registered products containing picaridin.
- A report of a completed field study by Carroll-Loye Biological Research of the mosquito repellent efficacy of a registered product containing Oil of Lemon Eucalyptus.
- Three closely related product-specific reports from a single completed field study by Carroll-Loye Biological Research of the mosquito repellent efficacy of four pesticides, all containing Deet.
- At the Board's request, discussion on the frequency and duration of exposure of subjects to potential mosquito landings.

In addition, EPA will report to the Board on its consideration of issues relating to the design of sampling strategies for handler research programs proposed by the Agricultural Handlers Exposure Task Force and the Antimicrobials Exposure Assessment Task Force II.

Finally, the Board may also discuss planning for future HSRB meetings.

B. Meeting Minutes and Reports

Minutes of the meeting, summarizing the matters discussed and recommendations, if any, made by the advisory committee regarding such matters will be released within 90 calendar days of the meeting. Such minutes will be available at http://www.epa.gov/osa/hsrb/ and http://www.regulations.gov.

In addition, information concerning a Board meeting report, if applicable, can be found at http://www.epa.gov/osa/hsrb/ or from the person listed under **FOR FURTHER INFORMATION**.

Dated: September 21, 2007.
George Gray,
EPA Science Advisor.
[FR Doc. E7-19125 Filed 9-26-07; 8:45 am]
BILLING CODE 6560-50-P

Attachment C

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
HUMAN STUDIES REVIEW BOARD (HSRB)
PUBLIC MEETING
OCTOBER 24-26, 2007

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-2007-0942

Wednesday, October 24, 2007

8:30 a.m. **Convene Meeting and Identification of Board Members**
Celia Fisher, Ph.D. (HSRB Chair)
8:40 a.m. **Welcome**
George Gray, Ph.D. (EPA Science Advisor)
8:45 a.m. **Opening Remarks**
Debbie Edwards, Ph.D. (Director, Office of Pesticide Programs [OPP], EPA)
8:50 a.m. **Meeting Administrative Procedures**
Paul Lewis, Ph.D. (Designated Federal Officer [DFO], HSRB, OSA, EPA)
8:55 a.m. **EPA Follow-up on HSRB Recommendations**
Mr. William Jordan (OPP, EPA)

Scientific and Ethical Approaches for Observational Exposure Studies
9:05 a.m. **EPA Draft Document *Scientific and Ethical Approaches for Observational Exposure Studies***
Roy Fortmann, Ph.D. (Office of Research and Development [ORD], EPA) and Larry Cupitt, Ph.D. (ORD, EPA)
10:15 a.m. **Break**
10:30 a.m. **Public Comments**
11:00 a.m. **Board Discussion**

One of the goals of the document is to identify the major scientific and ethical areas and issues that researchers should address in the design and implementation of observational human exposure measurement studies, with the emphasis on the areas requiring ethical considerations. Does each section identify the major areas and issues where ethical considerations should be addressed?

12:15 p.m. Lunch
1:00 p.m. Board Discussion (continued)

The document is intended to serve as a reference and resource of information that researchers can use in the design and implementation of observational exposure studies. Are there additional sources of information that should be considered for inclusion in the section?

Is the information presented accurately and clearly in each section?

Note: Board discussion will focus on responding to the three charge questions together by section (Sections 1 to 7) of the EPA draft document.

Sodium Azide
1:45 p.m. Science and Ethics of Sodium Azide Study
Ms. Nancy McCarroll (OPP, EPA) and Mr. John Carley (OPP, EPA)
2:30 p.m. Public Comments
2:45 p.m. Board Discussion

The Agency has concluded that this study contains information sufficient for assessing human risk resulting from potential acute and chronic exposure. Please comment on whether the study is sufficiently sound, from a scientific perspective, to be used to estimate a safe level of acute and chronic exposure to sodium azide.

Please comment on the following:

Is there clear and convincing evidence that the conduct of the study was fundamentally unethical?

Is there clear and convincing evidence that the conduct of the study was significantly deficient relative to the ethical standards prevailing at the time the research was conducted?

3:30 p.m. Adjournment

Thursday, October 25, 2007

8:00 a.m. **Convene Meeting**
Celia Fisher, Ph.D. (HSRB Chair)
8:05 a.m. **Follow-up from Previous Day's Discussion**
Mr. William Jordan (OPP, EPA)

Science Issues in Mosquito Repellent Efficacy Field Research
8:10 a.m. **Introduction**
Celia Fisher, Ph.D. (HSRB Chair)
8:20 a.m. **EPA Presentation**
Mr. William Jordan (OPP, EPA)
8:40 a.m. **Public Comments**
8:55 a.m. **Board Discussion**

Issue 1.

- What do data show about the variability of the time intervals between first and subsequent landings in mosquito repellent field trials?

- What is the current scientific understanding of how factors other than repellent efficacy could affect the likelihood that an initial event—a mosquito landing or mosquito bite—would be "confirmed" by another similar event within 30 minutes? Please address at least these factors:

  - Characteristics of mosquito populations
  - Characteristics of test sites
  - Characteristics of test subjects
  - Characteristics of test methods

- Can the impact of such factors on the likelihood or timing of an initial and confirming event be predicted? Can it be quantified?

Issue 2.

At its June 27 - 29, 2007 meeting the Board learned that different designs with different "length-biased" sampling for mosquito repellent field studies are in use. One design exposes subjects to potential mosquito landings for one minute of every 15 minutes; another design exposes subjects to potential mosquito landings for five minutes of every 30 minutes. The DFO is separately providing a CD containing the background materials for the June 27 – 29, 2007 HSRB meeting. The protocols are loaded on the CD. These designs have different "length-biased" sampling.

- What is the methodological rationale for the two different designs?

- Which design is used more widely in the field? Why?

- Can potential effects of variation in the pattern of intermittent exposure on the results of efficacy testing be isolated from the effects of other variables? If so, can the direction or magnitude of the effects be predicted? How might these influences be analyzed and accounted for in collecting, reporting and analyzing repellent efficacy data?

Issue 3.

Dr. Matt Kramer, a USDA statistician who has served as a consultant, has suggested that the precision of estimates of Complete Protection Time (CPT) in repellent testing could be significantly increased by defining a failure of efficacy as the mean time from treatment to a series of several landings or bites. He has stated:

> The precision of CPT increases when it is estimated beyond time to [First Confirmed Bite] FCB or FCLanding. How well CPT can be estimated depends on the distribution of so many bites beyond FCB. The number of mosquitoes that will bite (*n*) will determine results of the test. Each person in the field should be his/her own control; that way it is possible to know *n* per person, and reduce person-to-person variability.
>
> If using the mean time to the first 5 bites, the SE will decrease proportionally as *n* increases ($n = 5$ in this case). That is equivalent to an increase in the power of the test of 5 times. This method allows for detecting formulation differences near the CPT.

- Does this approach, indeed, increase the precision of estimates of CPT markedly without requiring additional subjects?

- If so, would this increased precision justify the incremental risk to the subjects resulting from their exposure to a greater number of mosquito landings?

- Is it practical to test long-lasting repellents to the point of five landings?

10:00 a.m. Break
10:15 a.m. Board Discussion (continued)

Completed Field Efficacy Studies by Carroll-Loye Biological Research: SCI-001 and WPC-001

11:15 a.m. EPA Science and Ethics of Completed Carroll-Loye Biological Research Studies SCI-001 and WPC-001
Clara Fuentes, Ph.D. (OPP, EPA), Mr. Kevin Sweeney (OPP, EPA) and Mr. John Carley (OPP, EPA)

12:15 p.m. Lunch
1:15 p.m. Public Comments
1:45 p.m. Board Discussion

SCI-001
Is this study sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy of the formulations tested against mosquitoes? Please comment specifically on:

> Whether participation in field testing by several subjects on the day after they had been treated with a different test repellent is likely to have affected the validity of the results for those subjects on those days.
>
> The effects of changes to the experimental design resulting in evaluation of repellents using fewer than ten subjects per treatment per day, followed by pooling of results by site for statistical analysis.

Does available information support a determination that this study was conducted in substantial compliance with subparts K and L of EPA regulations at 40 CFR part 26? Please comment specifically on:

> The decision to use a different test formulation in place of one of the test materials described in the protocol reviewed by the IRB, EPA and the HSRB.
>
> How to assess the ethical conduct of an insect repellency study involving multiple test formulations when there is an ethical deficiency in the conduct of the study with respect to one of the test formulations. If the ethical deficiency warrants not relying on the results of the testing with regard to one test formulation, under what circumstances (if any) does the ethical deficiency affect the acceptability of the results from testing the other formulations?

WPC-001
Is the research conducted under WPC-001 sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy of the formulation tested against mosquitoes? Please comment specifically on whether participation in field testing by several subjects on the day after they had been treated with a different test repellent is likely to have affected the validity of the results for those subjects on those days.

Does available information support a determination that the research covered by WPC-001 was conducted in substantial compliance with subparts K and L of EPA regulations at 40 CFR part 26? If the conduct of any part of SCI-001 is deemed not to substantially comply with the requirements of subparts K and L, please comment specifically on how to assess the ethical conduct of research conducted under WPC-001 in light of the fact that it was conducted at the same times and at the same places as the research covered under protocol SCI-001.

3:00 p.m. Break

Carroll-Loye Biological Research Insect Repellent Efficacy Protocols

SPC-001

3:15 p.m. **Science and Ethics of Carroll-Loye Protocol SPC-001**
Mr. Kevin Sweeney (OPP, EPA) and Mr. John Carley (OPP, EPA)

3:45 p.m. **Public Comments**

4:00 p.m. **Board Discussion**

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

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

SPC-002

5:00 p.m. **Science and Ethics of Carroll-Loye Protocol SPC-002**
Mr. Kevin Sweeney (OPP, EPA) and Mr. John Carley (OPP, EPA)

5:30 p.m. **Public Comments**

5:45 p.m. **Board Discussion**

If the proposed research described in Protocol SPC-002 from Carroll-Loye Biological Research is revised as suggested in EPA's review, does the research appear likely to generate scientifically reliable data, useful for assessing the efficacy of the test substances for repelling mosquitoes?

If the proposed research described in Protocol SPC-002 from Carroll-Loye Biological Research is revised as suggested in EPA's review, does the research appear to meet the applicable requirements of 40 CFR part 26, subparts K and L?

6:45 p.m. **Adjournment**

Friday, October 26, 2007

8:30 a.m. **Convene Meeting**
Celia Fisher, Ph.D. (HSRB Chair)
8:35 a.m. **Follow-up from Previous Day's Discussion**
Mr. William Jordan (OPP, EPA)

ICR Repellency Efficacy Protocol A117
8:40 a.m. **EPA Science and Ethics Reviews of ICR Protocol A117**
Mr. Kevin Sweeney (OPP, EPA) and Mr. John Carley (OPP, EPA)
9:15 a.m. **Public Comments**
9:30 a.m. **Board Discussion**

If the proposed research described in ICR's proposed picaridin protocol is revised as suggested in EPA's review, does the research appear likely to generate scientifically reliable data, useful for assessing the efficacy of the test substances for repelling mosquitoes of the genus *Culex*?

If the proposed research described in ICR's proposed picaridin protocol is revised as suggested in EPA's review, does the research appear to meet the applicable requirements of 40 CFR part 26, subparts K and L?

10:30 a.m. **Break**

EPA Update of AEATF and AHETF Research Programs
10:45 a.m. **EPA Presentation**
William Jordan (OPP, EPA)
11:00 a.m. **Public Comments**
11:15 a.m. **Board Discussion**

No Board Charge

12:30 p.m. **Adjournment**
Celia Fisher, Ph.D. (HSRB Chair) and Paul Lewis, Ph.D. (DFO, HSRB, OSA, EPA)

* 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.

Attachment D

DISCUSSION QUESTIONS FOR MOSQUITO REPELLENT STUDIES

The Human Studies Review Board (HSRB or Board) has discussed and provided advice to EPA on scientific and ethical issues related to the conduct of field studies to evaluate the efficacy of mosquito repellent products. The HSRB has reviewed both proposals for new field studies and the results of completed studies. The HSRB has noted that, although there are many similarities across studies, not all studies employ the same study design. The HSRB has identified several methodological issues for which additional background information would assist the Board in its evaluation of such studies.

BACKGROUND

Currently, EPA requires all pesticide products that claim to repel mosquitoes to provide data on the duration of efficacy under field conditions at two biologically distinct sites. These data are derived from human research with subjects who have been treated with the repellent formulations in the field. The Agency evaluates the duration of repellent efficacy for a subject by calculating the time from application of the repellent to the occurrence of an event indicating an efficacy failure. Historically, for field studies of mosquito repellency, EPA has used the "first confirmed bite" as an indication of efficacy failure on a test subject. Several recent studies have shifted to the "first confirmed landing with intent to bite;" EPA has accepted this alternative endpoint. A "confirmed landing" on a test subject is a mosquito landing followed by a second landing on the same subject within a specified period of time (usually 30 minutes) after the initial landing.

Field studies typically involve 6 – 10 subjects who have been treated with a defined amount of the test material. Each subject is then regularly and repeatedly exposed to ambient mosquito populations for a fixed interval of time until the subject experiences an efficacy failure followed by a confirmation with the specified period of time. Mosquito landing pressure (representing intent to bite) at a site is monitored by concurrently exposing untreated subjects to mosquito landings. A study is considered valid only if there are at least a specified minimum number of mosquito landings on untreated subjects during each exposure interval.

On October 25, 2007, the HSRB will discuss scientific aspects of the design of field studies to assess the efficacy of mosquito repellents. For this meeting the Board has requested consultants to provide specialized information or assistance to the Board. The Board is particularly interested in the frequency, duration and timing of exposure of subjects to potential mosquito landings. The Board requests each consultant to respond briefly to the series of questions below. Please send the responses to the HSRB Chair and Designated Federal Official (DFO) at least one week before the meeting—i.e., by no later than October 18. All responses will subsequently be provided to the other consultants, the HSRB members, and EPA staff for their review, and will be posted on www.regulations.gov under docket ID

number, EPA-HQ-ORD-2007-0942. HSRB consultants will be available at the meeting to discuss their responses and address questions from the Board. The questions for Board consultant consideration are provided below:

DISCUSSION QUESTIONS

- What do data show about the variability of the time intervals between first and subsequent landings in mosquito repellent field trials?

- What is the current scientific understanding of how factors other than repellent efficacy could affect the likelihood that an initial event—a mosquito landing or mosquito bite—would be "confirmed" by another similar event within 30 minutes? Please address at least these factors:

    - Characteristics of mosquito populations
    - Characteristics of test sites
    - Characteristics of test subjects
    - Characteristics of test methods

- Can the impact of such factors on the likelihood or timing of an initial and confirming event be predicted? Can it be quantified?

At its June 27 - 29, 2007 meeting the Board learned that different designs with different "length-biased" sampling for mosquito repellent field studies are in use. One design exposes subjects to potential mosquito landings for one minute of every 15 minutes; another design exposes subjects to potential mosquito landings for five minutes of every 30 minutes. The DFO is separately providing a CD containing the background materials for the June 27 – 29, 2007 HSRB meeting. The protocols are loaded on the CD. These designs have different "length-biased" sampling.

- What is the methodological rationale for the two different designs?

- Which design is used more widely in the field? Why?

- Can potential effects of variation in the pattern of intermittent exposure on the results of efficacy testing be isolated from the effects of other variables? If so, can the direction or magnitude of the effects be predicted? How might these influences be analyzed and accounted for in collecting, reporting and analyzing repellent efficacy data?

Dr. Matt Kramer, a USDA statistician who has served as a consultant, has suggested that the precision of estimates of Complete Protection Time (CPT) in repellent testing could be significantly increased by defining a failure of efficacy as the mean time from treatment to a series of several landings or bites. He has stated:

The precision of CPT increases when it is estimated beyond time to [First Confirmed Bite] FCB or FCLanding. How well CPT can be estimated depends on the distribution of so many bites beyond FCB. The number of mosquitoes that will bite (*n*) will determine results of the test. Each person in the field should be his/her own control; that way it is possible to know *n* per person, and reduce person-to-person variability.

If using the mean time to the first 5 bites, the SE will decrease proportionally as *n* increases ($n = 5$ in this case). That is equivalent to an increase in the power of the test of 5 times. This method allows for detecting formulation differences near the CPT.

- Does this approach, indeed, increase the precision of estimates of CPT markedly without requiring additional subjects?

- If so, would this increased precision justify the incremental risk to the subjects resulting from their exposure to a great?

- Is it practical to test long-lasting repellents to the point of five landings?