July 14, 2009

Minutes of the
United States Environmental Protection Agency (EPA)
Human Studies Review Board (HSRB)
June 24-25, 2009 Public Meeting
Docket Number: EPA-HQ-ORD-2009-0183
HSRB Web Site: http://www.epa.gov/osa/hsrb

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

Date and Time:	Wednesday, June 24, 2009, 9:30 AM – 5:30 PM Thursday, June 25, 2009, 8:30 AM – 4:30 PM (See *Federal Register* Notice – Attachment B)	
Location:	Holiday Inn National Airport, 2650 Jefferson Davis Highway, 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:	Sean Philpott, Ph.D., M.S.Bioethics
	Vice Chair:	Rebecca Parkin, Ph.D., MPH
	Board Members:	Janice Chambers, Ph.D., D.A.B.T. Dallas E. Johnson, Ph.D. Michael D. Lebowitz, Ph.D., FCCP Lois D. Lehman-Mckeeman, Ph.D. Jerry A. Menikoff, M.D. Linda J. Young, Ph.D.
Meeting Summary:	Meeting discussions generally followed the issues and general timing as presented in the meeting Agenda (Attachment C), unless noted otherwise in these minutes.	

Meeting Administrative Procedures

Dr. Paul Lewis (Designated Federal Officer [DFO], Human Studies Review Board (HSRB), Office of the Science Advisor [OSA], U.S. Environmental Protection Agency [EPA or Agency]) opened the meeting and introduced Dr. Sean Philpott as the HSRB Chair and Dr. Rebecca Parkin as the Vice Chair. Drs. Philpott and Parkin will serve for 6 months or less until a permanent chair and vice chair are appointed. Dr. Lewis also welcomed Drs. Martin Philbert and William Popendorf, and Prof. Alan Meisel, who served as consultants to the Board for this meeting. Consultants provide specialized knowledge and assistance but do not participate in the Board's deliberative process.

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

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

Introduction and Identification of Board Members

Dr. Philpott welcomed Board members, EPA staff, and members of the public to the June 24-25, 2009 HSRB meeting. He acknowledged the efforts of Dr. Lewis, Board members, and OPP staff in planning and preparing for this meeting. He acknowledged and thanked Dr. Parkin for serving as Vice Chair.

Welcoming Remarks

Dr. Kevin Teichman (Acting Science Advisor, OSA, EPA), welcomed Board members, EPA staff, and the public to the meeting. In his role as Acting Science Advisor, Dr. Teichman oversees Board activities and also serves as Deputy Assistant Administrator for Science in the Office of Research and Development. He thanked the Board for their efforts in preparing for the meeting and thoroughly reviewing the documents provided in advance of the meeting. He acknowledged Drs. Philpott and Parkin for serving as the HSRB Chair and Vice Chair, respectively.

At this meeting, the Board will review several studies of chlorpyrifos that involved intentional human exposure but were conducted before implementation of the Agency's expanded human studies rule (40CFR26). The Board will review a field study of picaridin effectiveness against biting flies proposed by Carroll-Loye Biological Research (CLBR). A completed laboratory study of picaridin effectiveness against stable flies, conducted by ICR Research, Inc. also will be reviewed. This protocol was reviewed positively at the Board's April 2008 meeting. The Board will discuss a pesticide handler exposure protocol involving pesticide mixers and loaders, proposed by the Agricultural Handlers Exposure Task Force (AHETF). Finally, the Board will discuss and approve its report from the February 2009 HSRB meeting.

Opening Remarks

Dr. Debbie Edwards, Director, OPP, EPA, welcomed HSRB members and consultants. She thanked the Board for providing useful advice to OPP concerning the design and conduct of studies involving intentional human exposure to pesticides. She thanked her EPA colleagues for their work in preparing for this challenging meeting; many changes occurred before the final agenda was prepared. EPA had initially planned to present four pre-Rule studies of chlorpyrifos, but determined that the fourth would not be used to serve as a point of departure for risk assessment activities and thus did not require HSRB review. The scope of the charge to the Board also has narrowed for the Kisicki et al. (1992) study. The Agency has concluded that this study does not meet the necessary ethical standards. However, the Agency has requested the Board review this study because EPA may wish to rely on the study in the future under criteria to protect public health by relying on otherwise unacceptable research per the Agency's expanded human studies rule (40CFR26). Depending on the Board's advice regarding the other two chlorpyrifos studies, the information contained within these articles might be sufficient for EPA decision making regarding chlorpyrifos registration. If the Kisicki et al. study is determined to be crucial to EPA risk assessment in the future, it will be reviewed during a future HSRB meeting.

Dr. Philpott acknowledged the efforts of Dr. Edwards and EPA to finalize the agenda. He also thanked Drs. Janice Chambers and Lois Lehman-Mckeeman for working with EPA to reformulate the charge questions.

EPA Follow-up on Pesticide-Specific HSRB Recommendations

Mr. William Jordan (OPP, EPA) described Agency progress on guidelines to inform topical insect repellency protocols. A draft of these guidelines was reviewed at the February 2009 HSRB meeting. The Board raised concerns about issues related to the number of subjects needed and statistical treatment of the data. Other smaller details also needed clarification. EPA continues to develop these guidelines and will make them available to the public and publish them as part of the guidance documents provided for researchers seeking registration of products with EPA. EPA has addressed most of the smaller issues raised, but is still working to address issues related to sample size and statistical analysis. EPA will clarify that the published document is not final and that further guidance will be forthcoming. The Agency also is seeking other sources of advice to address this issue. EPA will release an improved version of the existing guidelines for efficacy testing of topical repellents in the near future, although the draft is not finalized. The document is undergoing the final stages of review at EPA.

Chlorpyrifos Human Toxicity Studies

Introduction and Context

Mr. John Carley (OPP, EPA) introduced the chlorpyrifos human toxicity studies to be reviewed by the Board. He explained that the dates of the studies refer to both unpublished primary reports and published manuscripts. The work by Nolan et al. was performed in 1981-1982, but published in 1984. The report by Honeycutt and DeGeare includes field work

performed in 1991-1992 and published in 1993. The work described by Kisicki et al. was performed in 1998 and reported in 1999.

Dr. Anna Lowit (Health Effects Division, OPP) introduced EPA's review of three pre-Rule studies of chlorpyrifos. Chlorpyrifos is an organophosphate pesticide that was first registered in 1965. In June 2000, the technical registrants entered into an agreement with EPA to eliminate and phase out nearly all residential uses of chlorpyrifos. The human health risk assessment developed for this Interim Registration Eligibility Decision relied on adult cholinesterase (ChE) data from rodents and dogs. Human studies were not used to inform point of departure or uncertainty factors. The Honeycutt and DeGeare study to be reviewed by the Board was used to develop the worker exposure assessment.

A new risk assessment of chlorpyrifos is warranted because it is ready for re-registration review according to the 15-year review cycle under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) for registered pesticides; this review requires updated human health and ecological risk assessments. The Natural Resources Defense Council and Pesticide Action Network, North America have petitioned EPA to revoke all tolerances and cancel all registered uses of chlorpyrifos. A draft Science Issue Paper reviewed by the FIFRA Science Advisory Panel (SAP) in 2008 included a review of the new science from animals and humans in the context of human health risk assessment and focused on the effects of exposure in pregnant women, fetuses, and juveniles, who are thought to be more susceptible to chlorpyrifos. This increased susceptibility is based on differences in age-dependant metabolism, epidemiology studies in mothers and children, rodent studies that have evaluated non-cholinergic toxicities (i.e., behavior, learning, biochemical responses), and acetylcholinesterase (AChE) studies in pregnant rats, fetuses, and post-natal pups.

The work published by Nolan et al., which was performed to gather absorption, distribution, and excretion data, used a single oral dose and a single dermal dose exposure, and had as endpoints red blood cell (RBC) ChE inhibition, plasma ChE inhibition, and the principal chlorpyrifos metabolite 3,5,6-trichloro-2-pyridinol (TCP) in blood and urine. Honeycutt and DeGeare was an agricultural re-entry worker exposure study and measured RBC ChE inhibition, plasma ChE inhibition, and urine TCP. The Kisicki et al. study was performed to develop a no observable effect limit (NOEL) for RBC AChE inhibition, used a single oral dose, and measured RBC ChE inhibition, blood TCP, and urine TCP.

EPA intends to use the Nolan et al., Kisicki et al., and Honeycutt and DeGeare studies for bounding analyses, in which blood and urine data and AChE/ChE inhibition from the human experimental studies will be compared with data from animal studies and human epidemiology to develop and refine physiologically-based pharmacokinetic (PBPK) models. Current PBPK models include data from Nolan et al., but not from Kisicki et al., or Honeycutt and DeGeare. EPA will not use the data from these studies as a point of departure or to directly inform the inter-species uncertainty factor. The animal studies provide high-quality dose response data for ChE across many doses and life stages and is adequate for regulatory purposes and to serve as a starting point for extrapolation. The human studies lack dose-response information and do not address non-cholinergic toxicities. EPA will use the human deliberate dosing studies together with rodent administered dose and human epidemiology studies to perform bounding analyses

and develop bounding estimates. PBPK models are helpful for extrapolating exposure across exposure routes, species, and dose ranges. These models represent the anatomy and physiology of the rodent or human and provide simulations of biological processes, such as absorption, distribution, metabolism, and elimination. They are widely recognized as the "gold standard" in human health risk assessment.

The SAP was supportive of EPA's preliminary conclusions regarding the use of the information in the human-deliberate dosing studies for risk assessment, but not for directly establishing point of departure or uncertainty factors. The SAP agreed with the Agency's scientific analysis to compare the blood levels in the deliberate dosing and epidemiological studies and considered it critically important to use the information from the studies to "bound" the reference doses/concentrations. EPA also was encouraged to consider the use of a PBPK model to widen application of these bounding data for current or potential human exposures and for the final reference dose or reference concentrations.

Data from the Nolan et al. study provides a link between rat and epidemiologic data and has been historically used to interpret biomonitoring studies. It provides an estimate of dermal absorption and is used in current PBPK models for inter-species scaling. The Kisicki et al. study was used in Timchalk et al. (2002) to evaluate the PBPK model described therein; it is not used in current parameterization of the model. The study is not statistically strong because it analyzed only a single subject. In addition, the lack of plasma ChE measurements from the study decreases its utility and the form of chlorpyrifos delivery (capsule) may have reduced its absorption. The Honeycutt and DeGeare study will be used in combination with other available worker biomonitoring studies to evaluate a range of urinary TCP concentrations for workers. This study can provide a link from data on individual TCP levels to epidemiologic data to understand how the data compare.

Clarifying Questions

Dr. Philpott explained that EPA had asked the Board to provide a scientific perspective focusing on the reliability of the blood and urine ChE measures. The Board will not comment on Agency activities for bridging the data across animal and human studies or about the dosage study results in the Kisicki study.

Dr. Chambers asked why the Kisicki study was being considered if its data would be used only for validation of the PBPK model. Dr. Lowit answered that if the Agency wishes to use this model in the future, the validation of it using the Kisicki study provides a basis for confidence in that model. Dr. Lehman-Mckeeman inquired if the data validate the model despite the differences in absorption. Dr. Lowit responded that only one person in this study had measureable ChE inhibition and urine TCP; the Timchalk model focuses on that data. The Nolan study data fit better with data from rats.

EPA Science Assessment: The Nolan et al. (1982) and Kisicki et al. (1999) Chlorpyrifos Single Dose Studies in Human Volunteers

Dr. John Doherty (Health Effects Division, OPP) provided EPA's science review of the three studies; the Nolan and Kisicki studies were presented together. Both studies involve intentional exposure in humans. The Nolan et al. study was performed by Dow Chemical Company and enrolled 6 males. They used an oral dose of chlorpyrifos at 0.5 milligrams per kilogram (mg/kg) on a tablet and a 5 mg/kg dermal dose. The Kisicki study was performed by MDC Harris Laboratory in Lincoln, NE. This study enrolled 12 members of each sex as controls and 6 members of each sex as the dose group. The oral doses provided were 0, 0.5, 1.0, and 2.0 mg/kg in capsules; dermal exposure was not assessed. Nolan et al. used the Michel pH stat assay to assess ChE; Kisicki et al. used the automated Ellman assay. The plasma ChE and RBC AChE were consistent with the original method for the Nolan et al study. Plasma ChE was not assessed by Kisicki et al. and the Kisicki RBC AChE was consistent with values derived in other laboratories. Nolan et al. used gas chromatography to analyze chlorpyrifos and TCP and Kisicki et al. used gas chromatography/mass spectroscopy (GC/MS) for this analysis. Levels of quantitation in Nolan et al. were approximately 5 nanograms per milliliter (ng/ml) for chlorpyrifos and approximately 2.5-5 ng/ml for TCP; these values for Kisicki were 1-1.2 nanograms per grams (ng/gm) and 2-10 ng/ml, respectively. The reliability of the results for chlorpyrifos detection for both studies was fair. Nolan et al. detected chlorpyrifos (5-30 ng/ml) in 22 of 48 samples from participants receiving an oral dose and in 9 of 36 samplings (5-10 ng/ml) from participants receiving a dermal dose, including 7 ng/ml and 10 ng/ml in 2 samples at the 0 time point. There was poor temporal association with inhibition and chlorpyrifos was not detected in urine. Kisicki did not detect chlorpyrifos in participants receiving a dosage of 0.5 mg/kg. They detected chlorpyrifos in 6 of 156 samples (maximum 5.6 ng/gm) from participants who received 1 mg/kg and in 12 of 150 samples (maximum 18 ng/gm) from participants receiving 2 mg/kg. Chlorpyrifos was not present when the only subject presenting with ChE inhibition began to show inhibition. Chlorpyrifos also was not detected in urine. Detection of TCP peaked in blood between 2 to 24 hours after exposure and in urine between 3 and 9 hours after exposure in the Nolan study. At a dose level of 1 mg/kg, Kisicki et al. detected peak TCP in blood between 4 and 48 hours and in urine between 12 and 48 hours. Both studies showed significant variability in the percent TCP recovered in urine.

Basal values of plasma ChE inhibition (0.87 ± 0.09 to 1.42 ± 0.17) in the Nolan study were reasonable. All 6 subjects reached a maximum of 71 to 89 percent inhibition, but the time to peak inhibition varied between 6 and 24 hours. The maximum blood TCP (715-1430 ng/ml) was usually attained prior to maximum inhibition. Approximately 700-800 ng/ml TCP in blood was needed to achieve between 57 and 63 percent inhibition for 2 subjects; however, in 1 subject 996 ng/ml TCP was associated with only 30 percent inhibition. The correlation of urine (micrograms per hour (µg/hour)) TCP with blood (µg/ml) TCP and with inhibition was confounded because of differences in units and times of collection and ChE assessment.

Basal values for RBC AChE inhibition in the Kisicki study ($8,576 \pm 556$ to $9,165 \pm 709$) are reasonable. At levels of 1.7 to 5.6 ng/ml chlorpyrifos, no inhibition was observed. Blood TCP levels up to 1,300 ng/ml were not associated with inhibition. In 1 subject, urine TCP levels up to 15,323 ng/ml were not associated with inhibition. Only 1 subject showed RBC AChE

inhibition; this subject had the highest levels of gastrointestinal absorption. Inhibition begins to peak before chlorpyrifos and TCP in the blood and urine peak. This is due to the creation of an intermediate metabolite (chlorpyrifos oxon) that cannot be detected before TCP is synthesized.

Dermal dosing was performed only in the Nolan study. There was a borderline inhibitory effect on plasma ChE in 3 of 5 subjects, with a maximum 26 percent decrease. RBC AChE was not inhibited. A blood TCP of 122 ng/ml was associated with a 21 percent decrease in ChE but 36 ng/ml was associated with a 26 percent decrease; these numbers were not correlated. Recovery of TCP in urine for the dermal dosing phase was 1.02 ± 0.57 percent in 5 subjects receiving the 5 mg/kg dose and 2.6 percent in 1 subject who received the 0.5 mg/kg dose.

The Nolan study supports EPA use of a low dermal absorption factor. Both Nolan and Kisicki demonstrate that butyryl ChE is more sensitive than RBC AChE in humans. These data may support PBPK models and also may support "bounding." The data also demonstrate the variability in humans with respect to absorption of chlorpyrifos from the gastrointestinal tract. The technical assessment for ChE/AChE should be considered reliable in both studies as should the technical analyses for TCP in blood and urine. Both studies have limitations in analytical methods (less sensitive than in the epidemiology studies) and variability in TCP analysis. Comparisons between the Nolan and Kisicki studies are confounded by use of a tablet versus a capsule for dosing. Chlorpyrifos levels also were near the limit of quantitation and the reliability of the data was only fair. The Nolan study reported only 1 dose resulting in approximately 70 to 89 percent inhibition. These data do not establish a NOEL and are difficult to use to establish minimal levels of TCP associated with inhibition. Because TCP is reported in units per hour and Kisicki and the epidemiology studies report it in units per milliliter, the data are not easily compared. The Kisicki study does not include plasma ChE assessment and because only 1 subject showed RBC AChE inhibition, the usefulness of these data also are limited.

Clarifying Questions

Dr. Philbert noted that the TCP levels in urine appeared low and asked whether integrated blood and urine measures were more predictive of ChE inhibition. Dr. Lowit explained that the time course of TCP detection does not match exactly that of ChE inhibition because of differences in their slopes. Dr. Popendorf inquired if EPA had any information on how samples were processed and ChE measured. Dr. Doherty replied that this information was not available to the Agency.

Dr. Lehman-Mckeeman noted that TCP is present in urine as TCP glucuronide. It is difficult to determine if all studies used acid hydrolysis to release the glucuronide moiety and measured glucuronide specifically or not. If the Nolan and Kisicki studies did not treat their samples identically, comparing the measurements might not be valid. She asked whether acid hydrolysis was performed in the Kisicki study and whether TCP, TCP glucuronide, or both were measured in blood. Dr. Doherty agreed to check on whether glucuronide was liberated from TCP in these analyses.

Dr. Dallas Johnson noted that some of the statistical analyses in the Kisicki study seemed inappropriate. He questioned if EPA would use that information to model a response from the

Kisicki study. Dr. Doherty responded that only one person in this study showed evidence of ChE inhibition and EPA has not performed further statistical analysis of the data in the report.

EPA Science Assessment: Honeycutt and DeGeare Study (1993)

Mr. Wade Britton (Health Effects Division, OPP) presented the Agency's science assessment of the Honeycutt and DeGeare study. This study was conducted to determine exposure to agricultural workers during pruning and picking activities in California citrus corps. Chlorpyrifos (Lorsban 4E) was applied once at each of 3 study locations (5-6 pounds (lbs) active ingredient per acre). The study, which was conducted between 1991 and 1992, monitored 15 individuals; the individuals were workers and were in the field for typical durations. For the picking scenario, 5 individuals at 1 site were exposed 43 days after application. In the pruning scenario, 10 individuals (5 at each of 2 sites) were monitored; exposure occurred 2 days after application. Rain occurred at 1 of the pruning sites. This study used biological monitoring (urine collected for 4 days after exposure and blood sampled 1 day after exposure, with pre-exposure samples collected for both) and passive dosimetry (dermal and inhalation) to evaluate exposure to chlorpyrifos. Leaf surface residues also were taken as an environmental sample. Urine results were considered most relevant for bounding analyses.

Blood samples were analyzed for plasma and RBC ChE levels. Urine was analyzed for TCP and creatinine; TCP was used to calculate the chlorpyrifos body burden (estimated absorbed dose) and creatinine was used to evaluate completeness of sample collection. Depression of ChE activity from pre-exposure levels determined as part of the study was analyzed. Plasma ChE activity was depressed an average of 0.02 percent (±0.05) in pickers, -1.0 percent (±2.9) in pruners entering wet fields, and -3.4 percent (±12) for pruners entering dry fields. Average ChE activity in RBCs was depressed -0.01 percent (±0.05) in pickers, -11 percent (±5.3) in pruners entering wet fields, and -30 percent (±16) in pruners entering dry fields. Urine TCP measurements were 4.5 ±2.6 micrograms per liter (µg/L) in pickers, 29 ± 28 µg/L(wet fields) and 15 ± 13 (wet fields) in pruners.

The study monitored both urine and blood (plasma and RBC) in all workers, which is not typical of existing chlorpyrifos exposure studies. The workers were monitored while performing typical activities in production fields; however, the study was not statistically designed to define the relationship between TCP and ChE activity. In addition, TCP exposure can occur from many sources, which may confound exposure measures. Passive dosimetry techniques, such as hand washes, may have limited absorption of chlorpyrifos, leading to a potential underestimate of TCP and blood ChE activity. The Agency has concluded that this study represents the best source for occupational worker chlorpyrifos biological monitoring. The study provides urine, plasma, and RBC measures in the same individuals and monitored typical worker activities and durations of exposure.

Clarifying Questions

Dr. Michael Lebowitz asked if the absorption values had been calculated by the investigator, and if so, why they were different from those calculated by EPA. Mr. Britton explained that EPA considered different methods for analysis and chose a method that

incorporated background correction for TCP and creatinine based on the literature. Dr. Lowit added that creatinine correction can be calculated using different methods and EPA chose a method that shows range rather than absolute numbers.

Dr. Lehman-Mckeeman inquired if a single time point after exposure was sufficient to characterize inhibition of RBC ChE and whether including plasma ChE data would help. Mr. Britton replied that EPA would have preferred to see additional samples and the lack thereof is noted as a limitation of the study. Dr. Lowit added that the Agency also would have preferred that the study include plasma data and that this, too, limits the utility of the study. She explained that these data will be considered in the context of six to eight other studies, including epidemiological studies in which measurements were several orders of magnitude lower.

Dr. Chambers questioned why EPA chose to rely on this study and not others that might be similar. Dr. Lowit responded that this was the only worker exposure study that measured blood ChE that required Board review. Mr. Carley clarified that EPA had relied on ChE to measure exposure in the past. Under the Agency's human studies rule, if EPA relies on a pesticide human intentional dosing study that measures a toxic effect, the study must first be reviewed by the HSRB. Because this study does not measure a toxic endpoint, it was exempt from Board review. The study actually was designed to measure endpoints that could be interpreted as toxic. Other chlorpyrifos exposure studies did not measure ChE and thus did not require Board review.

Dr. Lowit referred to Dr. Lehman-Mckeeman's previous question regarding acid hydrolysis of samples. She noted that on pages 14-16 of the Kisicki document, the second aliquot of blood and the urine samples are described as being treated with hydrochloric acid. Dr. Lehman-Mckeeman noted that she had seen that data. Other studies report addition of a higher acid concentration and also heat the samples at high temperatures to ensure sample acidification for extraction rather than hydrolysis. The Kisicki et al. data do not indicate whether the samples were heated and thus it is not clear if glucuronide was released.

EPA Ethics Assessments: Three Pre-Rule Studies of Chlorpyrifos

Mr. Carley provided EPA's ethics review of the three studies. The Nolan et al. study was performed to define absorption, distribution, and elimination of oral and dermal doses of chlorpyrifos. The data contributes to the weight of evidence linking animal and human epidemiological data. The subjects participating in this study were 6 healthy males, all of whom were salaried Dow Chemical Company employees who were recruited through in-house advertisements. Women of child-bearing age were excluded by the Institutional Review Board (IRB). The endpoints collected were objective and there was no collection of subjective data; thus concerns about subject bias in reporting are minimal. The margins of safety were adequate because doses were based on earlier studies (although these studies were not specifically identified) and a pilot pre-test. Expected effects included inhibition of plasma ChE but not RBC ChE. No clinical signs were expected and the effects were anticipated to be reversible; these expectations were met during the study. There were no specific benefits to subjects, but the data were likely to contribute to improved understanding of chlorpyrifos fate and better

characterization of chlorpyrifos exposure and thus the study could be predicted to generate societal benefits.

The Nolan et al. study underwent two rounds of ethics oversight. The study was approved by the Dow Human Health Research Review Committee and the University of Michigan Committee to Review Grants for Clinical Research and Investigation Involving Human Beings. The approvals are documented and contain some gaps typical for research from this period. Subjects were provided with a copy of the protocol to review and were briefed on study objectives, chlorpyrifos properties, pilot phase results and study procedures, benefits (including free meals), confidential handling of data, and voluntary participation and freedom to withdraw. The subjects signed consent forms reporting that they had read the protocol and been briefed on the research. The subjects were not paid.

The applicable ethical standards for this study are the Declaration of Helsinki (1975) and FIFRA §12(a)(2)(P). Both 40 Code of Federal Regulations (CFR) §26.1703 (prohibiting involvement of children or pregnant or nursing women) and 40 CFR §26.1704 (describing EPA's ability to rely on pre-Rule data) apply to this study. There was no evidence to suggest that the research was inconsistent with the Declaration of Helsinki and evidence indicates compliance with FIFRA §12(a)(2)(P). No children or pregnant or nursing women were intentionally exposed. There is no clear and convincing evidence of significant deficiency relative to the prevailing standards of research conduct. If the data are deemed scientifically valid and relevant, there are no ethical barriers in FIFRA, 40 CFR §26.1703, or 40 CFR §26.1704 that would prevent EPA from relying on the Nolan study.

The Honeycutt and DeGeare study was a field study of agricultural worker exposure to chlorpyrifos conducted in response to EPA requirements; it was part of a larger project to monitor agricultural worker exposure to chlorpyrifos occurring during mixing and loading activities and re-entry. The study determined ChE activity and TCP residues for workers re-entering citrus groves under two situations: (1) orange pickers re-entering 43 days after chlorpyrifos treatment and (2) lemon pruners re-entering 2 days after treatment. The California re-entry limit is 35 days but pickers re-entered after 43 days because the crop was not ripe until then. The pruners were tested because these workers re-entered the field earlier and this allowed gathering of better exposure data; exposure levels were too low for accurate detection in the pickers. The data gathered contributes to the weight of evidence linking animal and human epidemiological data.

The subjects were experienced citrus workers. Recruitment was through a labor contractor who employed the workers, which may have influenced subject choice to participate; this method of recruitment and lack of randomization was common for exposure studies during the time period in which the study was conducted. Difficulties in finding qualified and willing subjects were reported and it also was difficult to find participants with no baseline TCP. To find unexposed participants, an unreported number of employees of the commercial applicator companies permitting use of their facilities by the study investigators provided boots and work clothing for analysis to estimate background contamination. These workers were not considered subjects of the research but should have been. Mingling of subjects in this and a companion study of chlorpyrifos handlers occurred.

The study posed no increased health risks to the workers who were performing their typical activities and wearing normal protective clothing. Unaddressed risks include heat stress from wearing the whole body dosimeters; however, the weather was cool, mitigating this risk. Differential risks for pickers and pruners were realized and the informed consent form (ICF) was amended to reflect this. There were no benefits to subjects, but there were likely benefits to Dow Chemical, EPA, and the California Department of Food and Agricultural (CDFA) (parent organization of the California Department of Pesticide Registration [CDPR]).

The protocol was reviewed by the University of California-San Francisco Committee on Human Research, brokered by CDFA/CDPR, as was standard at the time. The revised ICF was approved by an IRB before use, although some amendments affecting subjects may not have been reviewed by the IRB. Nonetheless, the ethics oversight was closer and better documented than is typical for worker exposure studies from this period. The subjects were briefed in Spanish and English. The ICFs used were approved by the IRB and included all required elements, but retained erroneous content from the companion handler study. The ICF discussion of margin of exposure (MOE) should have been revised for pruners. Despite these errors, the informed consent process and documents were above average for exposure studies in 1991-1992.

The applicable standards of conduct include California Code of Regulations Title 3 §6710 (September 26, 1988), which states that the health of the subjects will not be endangered, participants will be informed of potential risks, medical supervision will be provided, and recommendations by the Human Study Committee of the California Health and Welfare Agency will be incorporated. IRB approval of the study assumes that these requirements were met. FIFRA §12 (a)(2)(P), 40 CFR §26.1703 and 40 CFR §26.1704 apply.

Evidence indicates substantial compliance with the California standards and with FIFRA. There was active CDPR oversight and approval, IRB review and approval, and consent was voluntary and informed. Some protocol amendments should have led to further revisions to the ICF, but the conduct and oversight are documented more completely than was typical for occupational exposure studies from this time. There was no intentional exposure of children or pregnant or nursing women, the study was not fundamentally unethical, and there is no clear and convincing evidence of significant deficiency relative to prevailing standards. If the data are deemed scientifically valid and relevant, there are no barriers in FIFRA or to EPA's reliance on the Honeycutt and DeGeare study in actions taken under FIFRA, 40 CFR §26.1703 and 40 CFR §26.1704, or §408 of the Federal Food, Drug, and Cosmetic Act (FFDCA).

The Kisicki study was conducted to determine a NOEL for RBC ChE inhibition following a single oral dose of chlorpyrifos. The research was undertaken by Dow Chemical at its own initiative. The study determined RBC and ChE inhibition and chlorpyrifos and TCP residues in blood and urine. The data may contribute to the weight of evidence linking animal data and human epidemiological data.

The subjects were "non-institutionalized subjects consisting of college students and members of the community at large." More than the reported 60 subjects were involved. In response to a "standard advertisement," 140 candidates responded and were screened; 60 were

enrolled as primary subjects with 22 more as alternates. After extensive substitution occurring at the time of "check-in," 30 males and 30 females served as treated or control subjects. In the documents provided, an alternate who replaced a primary subject was identified by the same subject number as the person he or she replaced. The age range of subjects was 19 to 54 years, with a mean age of 31 years. There were few inclusion criteria but extensive exclusion criteria. Candidates were rejected at screening mainly because of the presence of drugs or other alterations in blood chemistry. Enrolled subjects were replaced by alternates mainly because a number of those enrolled did not show up at check-in.

The lowest dose (0.5 mg/kg) was chosen to overlap with data in the Nolan study. Because this dose showed no RBC ChE inhibition in the Nolan study, low and mid-doses (0.5 and 1.0 mg/kg, respectively) were administered concurrently in Phase 1. The investigators confirmed no effects at 1.0 mg/kg before increasing the dose to 2.0 mg/kg in Phase 2.

Risks to subjects were not discussed in the protocol. The ICF described potential side effects as including "improved performance on numerous tests of mental function." The ICF stated that no adverse effects were anticipated and that animal studies indicated little to no risk to humans. Subjects were informed that specific and effective antidotes were available and that in all but exceptional cases, those seriously poisoned recover rapidly and suffer no long-term effects. The ICF described risks involved in drawing blood. The form also contained this statement: "It may be very unsafe for me (the subject) to leave the clinic." The ICF noted that the procedure may be associated with undesirable and unpredictable effects, although in the opinion of medical consultants working for Dow Chemical's in-house IRB (MDS-Harris), those risks are not great enough to prevent participation. This information was placed just above the signature line.

To minimize subject risk, vital signs were taken periodically and subjects were asked open-ended questions about how they felt. Physicians were on call during subject confinement. The antidotes described were not required by the protocol to be available during testing, but information provided later indicated that the antidotes are always part of the crash carts kept in the clinic. The ICFs stated that the subjects would receive "no direct medical benefit" but that the information gathered "may provide potential benefit to others." The protocol does not discuss the potential societal value of the information. The relation of risks and benefits also were not addressed in the protocol or by the IRB.

The protocol, Material Safety Data Sheets (MSDS), consent form, payment, and recruiting advertisement were reviewed and approved by MDS-Harris. Additional changes were reported to have been submitted to the IRB directly from the sponsor and Amendment 1 and the revised ICF also was approved by the IRB. MDS-Harris IRB currently holds a Federal-Wide Assurance (FWA) from the Office of Human Research Protection (OHRP). An explanation of the research and signature of the consent form occurred during the "check-in" period, which took place the evening before treatment. The seemingly hectic circumstances surrounding check-in for such a protocol are unlikely to have provided the prospective subjects with sufficient opportunity to consider whether or not to participate. In addition, because of subject substitution occurring when participants did not show up, dose preparations had to be changed because dose was dependent on subject weight. Of most significant concern to EPA, all enrolled primary and

alternate subjects had provided blood and urine samples for screening and baseline measurements before receiving an explanation of the research or signing the ICF.

The ICF itself contained inappropriate technical language; the reading grade level for the first full paragraph was 17.7. The documents were poorly organized, contained pronoun shifts, and also contained a mix of dire warnings and soothing reassurances that were difficult to follow or understand. The discussion of risks was incomplete and misleading. The escalation rule was not explained to subjects, nor were the results of Phase 1 incorporated into the ICF for Phase 2.

Subjects were free to withdraw; two subjects withdrew. Subject privacy was not compromised in the reports. Although subjects were compensated, the recruiting and screening processes were needlessly intrusive. A surgical history was taken, but the information was not used. In addition, women were asked to certify that they were surgically sterile or using birth control, as well as to take a pregnancy test.

An unreported deviation occurred when the only subject with significant ChE inhibition was lost to follow-up 48 hours after treatment. The protocol stated that adverse events, whether serious or not serious, would be followed to resolution regardless of whether the subject was still participating in the study. This event was not acknowledged to be a deviation from the protocol.

The applicable standards of conduct are 21 CFR parts 50, 56, and 321; the Declaration of Helsinki (1966); and FIFRA §12 (a)(2)(P). The applicable standards of acceptability are 40 CFR §26.1703 and 40 CFR §26.1704. 21 CFR parts 50 and 56 require IRB oversight and prior approval, risk minimization, a favorable risk/benefit balance, acceptable informed consent process and ICF, equitable subject selection, and fully voluntary participation. The review and approval of the protocol by the MDS-Harris IRB did not show concern for or ensure compliance with these standards. The deficiencies in the consent process made conduct of the protocol non-compliant with FIFRA §12 (a)(2)(P). The most significant deviation was the collection of samples before consent was obtained.

EPA has concluded that the study did not involve intentional exposure of pregnant or nursing women or children. There is no clear and convincing evidence that the research was fundamentally unethical. Despite some gaps in the record, there is clear and convincing evidence that conduct of the Kisicki study was significantly deficient relative to the standards of 21 CFR parts 50 and 56, cited by the investigators as governing this work. Except under the provisions of 40 CFR §26.1706, EPA is forbidden to rely on this study in actions under FIFRA or FFDCA.

Clarifying Questions

Prof. Meisel asked if the records provided for the Nolan study indicated whether the Michigan IRB applied regulations prevailing before implementation of the Common Rule. Mr. Carley answered that he did not have this information. Prof. Meisel inquired if the IRB had experience in these types of studies. Mr. Carley explained that the Nolan study, which involved a single dose and measured absorption, distribution and excretion, was similar to many studies performed at the time and thus the IRB probably had experience. Prof. Meisel questioned

whether Dow Chemical had submitted the protocol for the Nolan study to EPA. Mr. Carley responded that the protocol had not been submitted to EPA, but in the future, EPA will specifically request protocols in situations such as this. Mr. Carley also clarified for Prof. Meisel that the subjects participating in the Honeycutt and DeGeare study were exposed to the same risks to which they were usually exposed during normal work activities.

Dr. Jerry Menikoff inquired whether the Kisicki study adhered to the Food and Drug Administration (FDA) Common Rule. Mr. Carley clarified that the FDA rule applies only to studies being submitted to FDA; the Kisicki investigators would not have been subject to FDA jurisdiction, but did cite FDA standards. The regulatory standards of acceptability refer to standards prevailing when the work was performed. EPA is comfortable that the FDA rule prevailed at MDS-Harris and is thus comfortable that the FDA rule was the appropriate prevailing standard. Dr. Menikoff noted that the study did not meet these standards because blood and urine samples were collected before the subjects signed the ICF. He requested clarification of other reasons why the study did not meet prevailing standards. Mr. Carley explained that the misleading and unintelligible ICF might have resulted in poorly informed subjects; the ICF was poorly written and organized, was confusing, contained misleading information, and did not accurately describe events that would take place during the protocol. Another deficiency would be the consent process itself, which was likely to have been chaotic and disorganized and not supportive of thoughtful informed choice. Dr. Menikoff noted that the investigators did discuss risks of ingesting the test compounds and asked whether the statement regarding low risk and full recovery significantly deviated from true risks. Mr. Carley replied that the misleading part of the risk discussion was the inclusion of "red herrings;" the ICF stated that full recovery is expected in cases of serious poisoning, but did not indicate an actual risk of serious poisoning occurring. The document also cited unknown medical experts stating that the existing risks should not prevent subjects from participating. The document thus was confusing and contained contradictory information.

Dr. Popendorf noted that the Honeycutt and DeGeare study might have privacy issues, such as including subjects' names and Social Security numbers (SSNs) in the report. Mr. Carley clarified that this information was not reported by the study authors, but instead was included by the secondary contract laboratory that performed the ChE analysis. He added that at the time the study was conducted, there was less sensitivity regarding SSNs than now.

Dr. Chambers inquired if ICFs were more consistent at the time the Kisicki study was conducted. Mr. Carley responded that this is one of the few ChE studies using a single rising dose. It is only one of two performed in the United States. Several ChE studies were performed in the United Kingdom; these also had ICF problems but were conducted in a more straightforward manner. The other U.S. study is similar to the Kisicki study and was conducted at approximately the same time in contract research organization laboratories performing drug studies. The Kisicki study is better than the others regarding consent. MDS-Harris was a high volume IRB and it is likely that this study differed in detail but was similar to other work reviewed by this IRB. MDS-Harris may have approached the study slightly differently because it involved use of a pesticide. Other ICFs for similar studies performed at the same time provided context for review of the Kisicki study.

Clarifying Questions for the Principal Investigator/Sponsor

Dr. Kenneth Racke, Dow AgroSciences and Dr. Craig Barrow, Science Policy Analysis, Strategies & Solutions

In response to Dr. Philpott, Drs. Racke and Barrow stated that they had no corrections or clarifications for EPA's science and ethics reviews.

Dr. Lehman-Mckeeman requested clarification regarding measurement of TCP versus TCP-glucuronide, particularly in the Kisicki et al. study. Dr. Racke explained that the analyses in the Kisicki study were conducted under the supervision of the Dow Method of Burzak (1978). An addendum submitted to EPA in 2000 contained all analytical details. EPA could make this report (Report B) available to the Board. Dr. Doherty clarified that this report was provided to the Board.

Dr. Johnson referred to the statistical analyses presented in Appendix 3 and noted that mixed model procedures were used and repeat measures analyses were performed using a SAS program. The repeat measures analyses were reported first and are incorrect; however, it appears that neither EPA nor Dow Chemical relied on these numbers.

Dr. Philpott noted that MDS-Harris has an FWA, but Mr. Carley was unsure of when it was acquired. Dr. Racke replied that he did not know when the FWA was acquired but could find out.

Dr. Popendorf inquired if the report on the ChE analysis performed by the MDS chemical laboratory in Toronto, Canada was similar to that presented in part C of the report but provided additional details. Dr. Racke responded that the only analyses reported were those reported in Kisicki et al.

Public Comments

Dr. Philpott invited oral public comment on the chlorpyrifos human toxicity studies. No oral public comments were presented.

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

Dr. Philpott opened discussion of the Board's approach for reviewing pre-rule human dosing studies. The Board developed these guidelines during the spring of 2006. At its May 2006 meeting, the Board determined several points of consideration for scientific review of pre-Rule studies. The work must be justified, e.g., the scientific question must be worth answering and use of humans should be necessary. Whether the risk posed to humans is serious or irreversible also should be considered. The Board also should determine whether the dose selection is appropriate and sufficient to answer the question; in most cases, a single dose would be insufficient. The doses also must be based on appropriate data such as animal data or

previous human studies. Endpoints must be consistent with the aim of the study and appropriate for answering questions about human response with the necessary sensitivity, validity and accuracy. The choice of participants must ensure that the population chosen is appropriate and will yield generalizeable data; appropriate exclusion and inclusion criteria also must be met. The proposed methodology must include an adequate sample size. The Board has previously been unsure that the sample size proposed in many of these studies is appropriate and will consider its previous recommendations to EPA. EPA also is re-examining its stance toward sample size and selection, but any changes in EPA guidelines will take time to be implemented. Control and experimental groups must be chosen thoughtfully and be sufficient to test the proposed doses. Data generated by these studies must be statistically analyzable and the analysis methods must be appropriate.

HSRB definition of single dose level studies describes an individual study that uses one dose level, irrespective of the number of subjects, frequency of dosing, or inclusion of a control or placebo. The Board has concluded that single dose level studies have limited utility and cannot be used in isolation to establish a no observed adverse effect level or low observed adverse effect level. A single dose level study may be useful if it is interpreted within the context of additional studies that provide information at other dose levels under analogous conditions; extrapolation from single dose studies is not recommended if there are significant differences in study design. Such a study also may have utility if it provides evidence of adverse effects observed at lower levels than other studies have indicated. Study utility will depend on the robustness and rationale of the study design.

40 CFR part 26, subpart Q describes the ethical standards for assessing whether EPA may rely on the results of human research in EPA actions. 40 CFR §26.1704 prohibits EPA reliance on unethical human research with non-pregnant, non-nursing adults conducted before April 7, 2006. 40 CFR §26.1703 constrains pre-Rule studies; EPA cannot rely on such studies that involved pregnant or nursing women or children. Several of the studies included in this meeting's discussion did not include children or pregnant or nursing women. The Board had planned to address the applicability of 40 CFR §26.1706, which provides criteria and procedures for EPA to rely on otherwise unacceptable research to make decisions to protect public health; however, after further discussions the Agency withdrew questions to the Board about relying on the Kisicki study if it was judged scientifically valid but unethical. Under this regulation, there are criteria and procedures to allow EPA to ask for Board guidance on how to use data if it is scientifically valid, but not entirely ethical.

40 CFR §26.1704 specifically prohibits use of data from a pre-Rule study if there is clear and convincing evidence that the conduct of the study was fundamentally unethical or if the study was significantly deficient relative to the ethical standards prevailing at the time. "Fundamentally unethical" is defined as research intending to seriously harm the participants or for which informed consent was not obtained. "Significantly deficient" research is defined as research that could have resulted in serious harm to the participants, based on knowledge available at the time, or a study in which the informed consent process was impaired.

Ethics have changed in the past 30 to 40 years, and the rules for human research also have changed. The challenge for the Board is judging pre-Rule studies in the context of the

standards and research culture prevailing at the time the study was conducted. Examples of prevailing standards include FIFRA Section 12(a)2(P), the Common Rule (40 CFR part 26), and the Declaration of Helsinki or other accepted International Codes of Research Ethics. There is some question about the applicability of the Declaration of Helsinki to studies that are not clinical in nature, but it was decided that the studies should be considered with the prevailing version of this guideline. EPA also has guidelines that allow the Agency and the Board to consider research from countries with procedures and regulations that differ from those in the United States, but these must provide the same protection as 40 CFR part 26, subpart K. The Common Rule applies to research conducted after 1991. If the study did not meet the ethical standards of the time, the Board must consider whether the research was fundamentally unethical or significantly deficient, as defined above.

Board Discussion

Prof. Meisel requested clarification regarding the two ways in which a study that did not meet the ethical standards of the time is judged, e.g., if the study was fundamentally unethical or significantly deficient. Dr. Philpott explained that at the time, these were the only situations considered. It is difficult to discern and consider the intent of researchers. Finding a study unethical requires determining whether the investigators knew participants would be harmed or if they deliberately misled participants. Dr. Philpott stated that, in his opinion, this standard is difficult to meet. Mr. Carley added that the criteria were developed based on recommendations from the National Academy of Science's (NAS) review of intentional dosing studies required by EPA. They recommended this compound decision-making standard for pre-Rule studies. If the study was not fundamentally unethical, EPA could still consider whether it was significantly deficient. He explained that the Common Rule was not automatically the prevailing standard for all work performed at the time, but only for work relied on by Federal agencies. The Rule existed at the time of the Honeycutt and DeGeare study, but was not the prevailing standard at the time.

Dr. Menikoff noted that not all Board members agreed that the statement regarding intent to seriously harm participants or failure to obtain informed consent fulfilled all ways in which a study could be fundamentally unethical. These statements are listed as examples in Board guidance and thus other examples of ways in which a study might be fundamentally unethical could exist. Dr. Philpott agreed that the statement might not be expansive enough and that a study could be ruled unethical for reasons other than those listed. He agreed to add an "e.g." to the Board's statement to indicate that these are examples and not the only conditions under which a study could be deemed unethical.

Dr. Linda Young noted that sample size considerations are made prior to study conduct. Once the study is performed sample size cannot be changed and thus the Board can only review the analyses. Dr. Philpott stated that not all judgments of scientific quality must meet the highest possible standards. He reminded the Board that pre-Rule studies will be different than those designed currently. The stated criteria are meant to guide discussions concerning whether the data are scientifically valid for EPA use.

Mr. Carley clarified the meaning of "clear and convincing evidence" as a term of art from the legal field, falling somewhere between "weight of evidence" and "beyond a shadow of a doubt." The criteria require positive evidence; gaps in reporting do not constitute clear and convincing evidence. Ironically, a well-documented study is more likely to contain "clear and convincing evidence" of flaws. He reminded the Board to distinguish between clear and convincing evidence and reporting discrepancies in its considerations. In response to a question from Dr. Popendorf, Dr. Philpott agreed that it was possible for a sponsor to refuse to release incriminating documents, but previous experience has shown that sponsors provide the Board with as much information as possible. The only example of insufficient information arose during review of a study conducted in 1953, in which materials documenting voluntary and informed consent were destroyed in a fire. This presented a challenge to Board review, but was not deliberate withholding of data. The Board could not conclude that there was positive evidence of significant ethical deficiencies.

With regard to the chlorpyrifos toxicity studies reviewed at this meeting, Dr. Philpott reminded the Board to focus on whether the data presented in the studies could be used by EPA for decision-making purposes.

Scientific Considerations – Nolan et al. (1982) Study

Are the blood and urine measurements of chlorpyrifos and/or TCP from the Nolan et al. oral and dermal studies reliable?

Dr. Lehman-Mckeeman opened the science discussion of Nolan et al. by explaining that when she reviewed these data, she focused on judging its reliability. For all studies, she determined whether the administered dose could be confirmed; if the samples were collected in a manner that would provide reliable data; and if the analytical methods used were reported in such a way to allow her to determine whether the data were reliable and valid.

The Nolan study is a single dose study with the explicit purpose of comparing the fate of chlorpyrifos administered orally versus dermally and to address absorption by two routes. The study was small, involving only six subjects; one subject received a dermal dose different from that received by the other five. The oral dose was delivered by dissolving chlorpyrifos in methylene chloride and pipetting the solution onto a tablet and confirming weight; there is no evidence reporting the weight of the tablet before the dose, but Dr. Lehman-Mckeeman assumed this procedure was performed correctly. Subjects were kept in the clinic for 48 hours, which permitted the first few samples to be collected reliably. After this time, the quality of sample collection is unknown and creatinine measures were not normalized. Description of gas chromatography did not include information on derivatization, but did state that hydrolysis was used to analyze conjugates.

EPA states that chlorpyrifos levels in blood and urine were at or below the limits of detection, but the study defines "limits of detection" differently than how these are currently defined. Dr. Lehman-Mckeeman agreed with EPA's findings that the measurements are not highly reliable. It is difficult to confirm the dose administered, but the presence of TCP above baseline limits indicated it was, and the methods used for measuring TCP are appropriate for the

1980s. The data for urinary TCP are reliable and show a difference between oral and dermal dosing. Thus, the urinary TCP data are reliable.

It is unclear whether blood TCP levels are useful. The investigators appear not to have analyzed the conjugated metabolite, and thus the accuracy of the blood TCP levels cannot be determined.

Dr. Lehman-Mckeeman concluded that the data on chlorpyrifos levels are not useful or informative. Although reported as a rate and not normalized to creatinine, the urinary TCP data are reliable.

Dr. Parkin agreed with Dr. Lehman-Mckeeman's assessment. She added that the small sample size and selection of only male subjects raised questions about the generalizability of the data. Inclusion and exclusion criteria are implied, but not clearly stated. She agreed with Dr. Lehman-Mckeeman regarding the reliability of the results and whether they could be reproduced; however, when used in the context of other studies, the urinary TCP analysis results could have value.

Dr. Popendorf inquired if any pre-exposure analyses of urinary TCP were conducted as part of this study. Dr. Lehman-Mckeeman responded that there were no controls and no pre-dose samples demonstrating undetectable levels of TCP. This is a limitation of the study. The oral dosing data suggest that approximately 70 percent of the dose was recovered in urine, indicating that TCP measured in urine probably was not primarily background. She agreed that the lack of pre-study measurements hinders analysis of recovery and erodes, but does not necessarily negate the utility of the study.

Dr. Philpott stated that the Board consensus was that TCP levels in urine are reliable, but it is not clear if blood levels are useful because of uncertainty regarding whether the analytical methods used accurately detected TCP conjugates. The Board also has concerns about chlorpyrifos measurements because they are too close to the limits of detection and suggests that these are not reliable for EPA use.

Are the measurements of ChE activity/inhibition from the Nolan et al. oral and dermal studies reliable?

Dr. Lehman-Mckeeman explained that the method used in Nolan et al. to analyze ChE activity can have day-to-day measurement variability (as much as 10 to 15 percent). This effect can be controlled by performing 2 or 3 pre-test collections and analysis of RBC ChE activity. The variability observed over the course of time for which the samples were taken is consistent with what was reported in the literature. The authors reported a decrease in plasma ChE activity consistent with dosing, but no change in RBC ChE activity. Although there was no concurrent control, pre-treatment analyses with more than 2 replicates was performed. Dr. Lehman-Mckeeman concluded that the data provide reliable measures of plasma and RBC ChE activity.

Dr. Philbert generally concurred with Dr. Lehman-Mckeeman's conclusions; however, he was concerned that there was no record of ethnicity or diversity of ethnicity; certain ethnicities

likely were oversampled, so the results may be misleading. Mr. Carley reported that all participants were white. Dr. Philbert withdrew this issue.

Dr. Philbert commented that reporting of the dose on a quantity mass basis rather than as meters-squared, as is usual for clinical studies, was unusual. This will complicate comparison and correlation of data gathered from work performed in other species, in which surface area is used to report dose.

Dr. Popendorf noted that RBC ChE methods are traditionally susceptible to day-to-day laboratory variation. A 10-percent group shift due to laboratory methodology might be acceptable when monitoring for an acute situation (greater than 30 percent drop in ChE activity) but laboratory control should be maintained if smaller exposures are expected. The laboratories should have used an unexposed group to detect a shift in values that could be used to inform normalization for the exposed group. None of the three studies discussed at this meeting used a control, which is problematic because only low levels of inhibition were detected. The spurious change in levels reported in one of the studies is characteristic of day-to-day assay variation. He concluded that the RBC measurements probably were not reliable.

Dr. Philpott questioned whether the Board consensus was that data on plasma ChE inhibition are reliable but there were concerns about day-to-day variation inherent to the analysis technique. This is particularly of concern for analysis of ChE inhibition in RBC. The lack of a control group also was problematic. He asked if the Board would recommend that although the plasma data are reliable, EPA should consider not using the RBC data.

Dr. Chambers commented that the RBC data were not as robust as the plasma data, but not entirely unreliable. Dr. Popendorf referred to the analysis of RBC data by EPA presented in Tables 4 and 5 of the data. Initially, RBC ChE levels associated with the oral dose are above baseline; by Day 4, the group as whole has dropped 30 percent and then 3 of the 5 subjects show activity above normal levels the next day. The RBC data lacks consistency and shows evidence of activity shifts unrelated to time after exposure. Dr. Lehman-Mckeeman stated that she concluded from these data that the dose administered had no effect on RBC ChE activity and asked whether Dr. Popendorf thought that this could not be concluded because of the variability. She continued by noting that the plasma data clearly showed strong inhibition. Despite significant variability, the RBC data showed no clear effect within the range of variability. Her conclusion was to suggest that there was no observable effect on RBC ChE activity.
Dr. Popendorf conceded this point.

Dr. Philpott asked Dr. Lehman-Mckeeman to formulate the Board consensus to address this issue. Dr. Lehman-Mckeeman suggested that the Board state that it recognizes the variability in these data and that any changes could be confounded by this variation or no effect exists. Dr. Chambers added that in rats, if levels of inhibition are within the constraints of variability, inhibition cannot be assumed. She agreed with Dr. Lehman-Mckeeman's interpretation of the data.

Dr. Philpott concluded that the plasma ChE data for this study are reliable. The Board recognizes the variability inherent to the RBC data and concludes that there appears to be no

inhibition of ChE activity in RBCs. The Board is comfortable with EPA using the data as evidence of no significant RBC ChE inhibition at this chlorpyrifos dose.

Ethical Considerations – Nolan et al. (1982) Study

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

Dr. Menikoff emphasized the need for the Board to consider only standards applicable at the time the research was conducted, which will usually mean erring on the side of allowing use of the data. He stated that the Nolan study was not fundamentally unethical; there is no evidence of intended harm and informed consent was obtained. Regarding whether the research was significantly deficient relative to the standards of the time, in 1982 when the study was conducted, the prevailing standard was FIFRA. The study was reviewed by two IRBs, informed consent was obtained, and it was a low-risk study. Dr. Menikoff concluded that Nolan et al. (1982) was not significantly ethically deficient and that EPA could rely on the data.

Prof. Meisel agreed with Dr. Menikoff, but expressed concern that the protocol was not provided to the Board; thus, it is not possible to know exactly what subjects were told regarding the protocol during the consent process; however, because the standard calls for erring on the side of inclusion, Prof. Meisel agreed that EPA could rely on the data.

Dr. Philpott summarized that the conduct of Nolan et al. met the ethical expectations of the time. The study was not fundamentally unethical or significantly ethically deficient. The Board has no objection to EPA relying on the data, but notes that including the protocol for review would have aided Board deliberations.

Scientific Considerations – Honeycutt and DeGeare (1993) Study

Are the blood and urine measurements of chlorpyrifos and/or TCP from the Honeycutt and DeGeare worker biomonitoring study reliable?

Dr. Lehman-Mckeeman opened discussion of this study by stating that its objective was to determine exposure in agricultural workers re-entering a treated field. The study emphasized whole body dosimetry and biomonitoring. She began by assessing the reliability of the data. Dose cannot be confirmed because the purpose of the study was to determine dose. Thus, she focused instead on the overall reliability of ChE, chlorpyrifos, and TCP quantitation by judging the accuracy and validity of the analytical methods used and the reliability of sample collection.

The analytical method used was GC/MS using trimethyl silane derivatives to monitor TCP. The authors reported a limit of detection as three times the signal-to-noise ratio. The methods used for this work are generally adequate. The report also specifically addresses the glucuronide issue by specifically reporting the acidification and derivatization processes used.

Regarding the reliability of sample collection, the investigators attempted to obtain pre-exposure samples and should be commended for this; however, all pre-exposure samples had detectable TCP, although workers were instructed not to enter treated areas. Chlorpyrifos levels in pre-exposure samples were essentially non-detectable. This information raises the issue of the extent to which pre-exposure TCP levels influence the accuracy of the results. In addition, it is unclear whether urine sample collection was complete. The study authors report 6 different methods for calculating dose and thus report a spectrum of dose values. The sample size for this work was 5 pickers and 10 pruners. Environmental conditions (unseasonably cool) modified exposure.

Dr. Lehman-Mckeeman stated that determining the acceptability of these data was difficult, because the study could not be considered in isolation. The Nolan study supports the results of this study. Measuring TCP in urine is a reasonable way to determine chlorpyrifos exposure and thus the Honeycutt and DeGeare data might be acceptable; however, there is uncertainty regarding the extent of chlorpyrifos exposure attributable to the study itself or to exposure before or after the day of monitoring. Dr. Lehman-Mckeeman commended that the range of methods used to try to correct for sample collection issues, but this only added to the uncertainty regarding which numbers were valid. She concluded that the data are of limited utility. The analytical values determined are probably correct, but it is unclear how these values relate to true exposure.

Dr. Lebowitz questioned the investigators' choice to store urine samples at ambient temperature for 2 days and how this might have affected TCP quantitation. In addition, the first void might not have been collected correctly and insufficient numbers of samples were collected. He also had questions concerning the timing of blood collections.

The calculations to determine exposure using creatinine excretion and amount of chlorpyrifos absorbed appear rational, but differ from the methods used in the other studies. The lack of correction for background exposure levels is troubling. The conclusions drawn using the adjustment of TCP values using creatinine values do not appear to be appropriate. Dr. Lebowitz also questioned the usefulness of chlorpyrifos background calculations given the significant differences between adjusted chlorpyrifos numbers and kinetic modeling results. EPA also should consider the differences in the proportion of exposure related to dose.

Extrapolation of these data is possible using national exposure assessment surveys. EPA should refer to a white paper on this topic authored by the National Health and Nutrition Examination Survey. The authors used only a single biomarker, but others for chlorpyrifos exist and have different pharmacokinetic relationships. EPA should consider using these biomarkers to detect other sources of exposure in EPA-funded exposure biomarker studies.

Dr. Lebowitz concluded that the urinary excretion data could be used by EPA. He recommended that EPA use values that were adjusted for background exposure.

Dr. Chambers noted that the presence of TCP in workers before the experiment was to be expected since chlorpyrifos is widely used. How to account for this background exposure and interpret the data in light of it should be discussed, but the background exposure itself is

not surprising. Dr. Popendorf stated that the presence of background levels introduces significant uncertainty to the data and the effect of background on calculated exposure levels should be considered.

Dr. Popendorf referred to the results in Table 1. These results show significant variability of creatinine across different days and indicate that complete urine collection did not occur. If the numbers varied because of incomplete collection, the range of the standard deviation of the mean could indicate the degree of incompleteness; in this case, it appears that the results were only 20 percent complete. The analytical methods used were appropriate, but the investigators appear to be trying to use the data in a way not intended by the study design. Dr. Johnson cautioned that the study design appears to define 3 separate studies with 5 participants in each study; this would affect how the data can be used.

Dr. Philpott summarized that the Board found the data analysis to be valid, but had concerns about its utility because of background TCP levels and doubts concerning whether the urine collection was complete. Questions about the variability of the data also were raised. He asked if the Board would thus recommend that EPA not rely on the data without considering the background issues and incomplete urine collection. Dr. Chambers countered that the Board did not find that the data could not be relied on, but that the there are limitations to its use. Dr. Philpott suggested that the Board conclude that the data are reliable but of limited utility because of the small number of participants, variability in the data, and background and urine collection issues.

Are the measurements of ChE activity/inhibition from the Honeycutt and DeGeare worker biomonitoring study reliable?

Dr. Lehman-Mckeeman noted that although the methods used in this study are different from those used by Nolan et al., the same variability issues arise. Honeycutt and DeGeare did not use an untreated control; they collected pre-study "baseline" data, but exposure prior to participation in the study probably occurred.

The study reports data from RBCs from two points before field work occurred and at one point after exposure; this is less than ideal and collecting data at additional time points would have improved the quality of the data. Dr. Lehman-Mckeeman agreed with Dr. Johnson's comment regarding judging this work as three separate studies with very small sample sizes (N = 5).

The exposure occurring during this study probably was low, and thus little effect on RBC ChE was expected. The study was designed to assess dosimetry and biomonitoring rather than ChE levels; no correlation between exposure and ChE levels was observed. The utility of these data is questionable, given that exposure levels are lower than those observed in the Nolan study. Dr. Lehman-Mckeeman conclude that the data are well analyzed, but of limited use for providing information about the effects of chlorpyrifos.

Dr. Popendorf agreed with Dr. Lehman-Mckeeman's assessment of the study. He noted that ChE levels were monitored as a safety feature, but the focus of the study was to determine

dose and assay chlorpyrifos levels in urine. The data are not reliable for quantifying ChE inhibition as an effect of chlorpyrifos exposure.

Dr. Philpott asked if the Board consensus was that the ChE data are not reliable. Dr. Chambers countered that the data are as reliable as possible for a study of this type, but are of questionable use. Dr. Lehman-Mckeeman agreed that she did not question the validity of the data, but having only a single time point significantly impairs its utility. It is unclear how EPA will be able to use the data. Dr. Lowit clarified that if the Board finds the data unreliable, EPA cannot use it for any purpose. The Agency wishes to use the data in conjunction with other data to understand its limitations and to help determine bounding for levels of TCP that might be detected in the urine of exposure workers.

Dr. Philpott clarified that the Board found the data reliable, but had concerns about its utility with respect to how EPA plans to use it. Dr. Lebowitz expressed concern about the definition of "reliable data." He noted that Dr. Lehman-Mckeeman raised questions about data accuracy and validity. The analyses appear to be valid, but accuracy, precision and reliability are different. The experiment is not replicable and employed a small number of subjects and thus does not represent a universe of values that would be reliable. He concluded that the utility of the data would be very limited. Dr. Lowit noted that there is a distinction between the questions the Board has raised and EPA decisions regarding how to build the weight of evidence and evaluate the utility of the data and how it will be used. The Agency has not presented a great deal of information concerning its intended use of the data. Mr. Jordan clarified that HSRB comments about validity and the accuracy of measurements of different endpoints helps with EPA decision making, as do the Board's assessment of limitations on making generalizations from the data related to issues surrounding sample size, completeness of urine collection and the timing of sample collection. He explained that Dr. Lowit was describing how these data are part of a larger body of information, most of which was not presented at this meeting. EPA wishes to use the data appropriately, given Board comments about its limitations. Dr. Philbert noted that if the data are reliable, it should be possible to repeat the experiment and obtain the same results; it is unclear if this is the case for this study. Dr. Chambers warned the Board to be cautious about concluding the data are not reliable because the Board has not reviewed the other data that will be used in conjunction with these data, and also does not know exactly how EPA will use the data. The limitations of the study are obvious, but repeating a field study may not always generate the same results in many cases.

Dr. Philpott clarified that EPA is seeking advice regarding the accuracy of the data in terms of its collection, but recognizes Board concerns about its utility. EPA has had discussions with the SAP regarding how to use these data in conjunction with other similar data, but is not yet exactly sure how the data will be used. The Board should determine whether, in the context of how the study was conducted, the numbers generated are valid, and also should be cognizant of the data limitations; EPA should take these limitations into consideration when incorporating these data into the weight of evidence. He proposed as the Board consensus that the data are accurate and reliable but concerns about utility remain.

Ethical Considerations – Honeycutt and DeGeare (1993) Study

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

Dr. Menikoff stated that there was no evidence of intention to harm and informed consent was obtained; thus, the study is not fundamentally unethical. California state regulations represented the most stringent standards of the time. The study was reviewed by an IRB and an ICF was signed. He agreed with Mr. Carley regarding factual errors in the materials, but considered that these would not seriously impair consent. Dr. Menikoff also raised concerns about the degree to which the study was voluntary, but the study met relatively high standards concerning work using agricultural workers done at that time. He concluded that, from an ethics perspective, EPA can use these data. He commented that the release of SSNs was inappropriate, but not unethical.

Prof. Meisel agreed with Dr. Menikoff's summary. He noted that the subjects were vulnerable to employer coercion, but would have been exposed to the test pesticide in the course of their normal activities; thus they would have been exposed despite declining to participate in the study.

Dr. Philpott summarized that the Honeycutt and DeGeare study met ethical standards sufficiently to allow EPA to rely on the data.

Scientific Considerations – Kisicki et al. (1999) Study

Are the blood and urine measurements of chlorpyrifos and/or TCP from the Kisicki et al. oral study reliable?

Dr. Lehman-Mckeeman stated that the objective of this study was to determine the effect level for inhibition of ChE in RBC in humans and better define the pharmacokinetics of this inhibition. This was an escalating dose study and the dosing schedule appears to be well characterized and reported. Chlorpyrifos was added to a capsule filled with lactose powder and thus the administration differs from that described in Nolan et al. The study investigators provided a clear record of the weight of the capsule. Dr. Lehman-Mckeeman conceded Mr. Carley's point concerning the substitution of subjects and how this may have complicated ensuing appropriate dose based on subject weight, but concluded that the record keeping was sufficient to ensure that dosing was correct.

The study involved 60 subjects. Of these, 48 provided all periodic urine samples and 19 were complete based on urinary creatinine levels. The subjects stayed in the clinic for 48 hours and then were followed for up to a week. Some of these data are incomplete, but this does not limit the utility of the study.

Analysis involved derivitization and GC/MS similar to the Honeycutt and DeGeare study; however, the Kisicki study did not report specifically how acid hydrolysis was carried out.

In the report, the standards used are derivatives of TCP and include stable isotopes; TCP-glucuronide was not used to generate standards. Silanization is standard for analyzing hydroxyl groups and is used to analyze glucuronides. Dr. Lehman-Mckeeman noted that the report could have provided a better sense of what was measured. This is important because of the way that chlorpyrifos was administered. In this study, absorption was only 50 percent of that reported in the Nolan study. The Kisicki study authors contend that the way they administered the chlorpyrifos precluded absorption; the physical form of the dose can affect bioavailability, but a 50 percent difference seems larger than would be expected. This complicated determining if the results are different because of the analytical method used or because of the dosing form. Dr. Lehman-Mckeeman concluded that, to the best of her knowledge, the dose appears to be accurate and some of the data are incomplete, but the data can still be deemed reliable. She added that the discrepancies between this and the Nolan study, in addition to missing information concerning the analytical methods used are troubling. She encouraged EPA to precisely determine what was measured in this study. The data suggest differences in bioavailability between chlorpyrifos administered in a gelatin capsule or administered on a lactose tablet; this is unexpected.

Dr. Parkin agreed with Dr. Lehman-Mckeeman's assessment, particularly concerning the greater than 50 percent difference in absorption between the Kisicki and Nolan studies. She added that the use of alternate subjects also was of concern. She agreed that although the measurements were probably accurate and reliable, EPA should be cautious about how the data are used. Dr. Parkin was concerned about the lack of information about methods and other matters, the loss of the one subject who showed a response, and the variability of TCP concentrations in blood and urine that overlapped across doses; this variability raises further questions regarding appropriate use of the data.

Dr. Johnson noted that some of the analyses did not appear appropriate, particularly the repeated measures and analysis of variance (ANOVA) calculations in Appendix 3. On page 53, the authors provide a partial correlation matrix between measurements made at different time points within and across subjects. The correlation between 72 hours and 96 hours after dosing appears too close to be true. For the 2-hour and 4-hour time points on day 4, it should be possible to compute variance by dividing by degrees of freedom, but none of the data reported in the data tables has sufficient significant digits. The results from the ANOVA analysis also appear to be incorrect. Another model analysis provided appears to be reasonable, but it is not possible to tell which variables actually were analyzed. He recommended that EPA not rely on the analyses presented in Appendix 3.

Dr. Philpott summarized that the Board found the dose data to be accurate, but raised issues concerning the completeness of sample collection. Discrepancies were observed in the analyses, such as a lack of specific information about the hydrolysis process, absence of TCP conjugate controls, and discrepancies in absorption between this and the Nolan study. In the absence of additional information, the Board recommended that EPA use the data cautiously in light of the large amount of variability and uncertainty.

Are the measurements of ChE activity/inhibition from the Kisicki et al. oral study reliable?

Dr. Lehman-Mckeeman noted that this study assessed ChE only in RBC. Two pre-dose samples were obtained from each subject, and samples were collected 2 hours after exposure and for as long as 1 week. Untreated control samples were analyzed concurrently with experimental samples; thus, the assessment of ChE activity was relatively comprehensive. The small sample size does not undermine the data. The study increased to a dose of 2 mg/kg because the 1 mg/kg dose had no effect. At 2 mg/kg, an effect on ChE activity was observed in 1 subject, but this subject was lost to follow-up 48 hours after dosing. Because of the variability of the data, it was not possible to determine whether changes in ChE activity observed in other subjects were real or spurious; the investigators judged these changes to be spurious, based on the day-to-day variability inherent in the assay.

Dr. Lehman-Mckeeman concluded that the data are reliable, although she cautioned EPA regarding the incomplete profile for the subject who showed a change in ChE activity.

Dr. Chambers agreed with Dr. Lehman-Mckeeman's assessment. The erroneous chlorpyrifos measurements do not affect the RBC data. Changes in plasma ChE activity are not considered an adverse effect and thus these data were not collected. The variability was within the range of what is expected, given that the technique used to assess ChE activity in RBCs is not particularly sensitive. Given the normal range of variability, requiring a reduction in activity of at least 20 percent to determine inhibition is likely valid. She agreed that the data could be used to validate other data, but would not be appropriate for development of PBPK models.

Dr. Popendorf noted that, given the variability of the assay, he thought that only the peak inhibition values obtained from the group receiving 2 mg/kg chlorpyrifos (reduction in ChE activity of approximately 8-9 percent) were reliable.

Dr. Philpott summarized that the Board found the data to be reliable, but cautioned EPA on how it will use the data from the sole respondent who was lost to follow-up. Dr. Young added that the data should be re-analyzed; EPA should not rely on the analyses presented by the study authors. Dr. Philpott agreed to add this to the consensus. He also recommended that EPA consider repeating the statistical analyses correctly, given the concerns raised by Drs. Johnson and Young. Dr. Doherty noted that when EPA initially reviewed the study, the Agency decided that it was not necessary to re-analyze the data because only one participant showed a significant difference in ChE activity over time. Smaller differences were observed in other participants, but inhibition was not sustained over time. EPA could not conclude that inhibition occurred in more than one participant. Dr. Lowit added that EPA would re-assess the analysis in Appendix 3 mentioned by Dr. Johnson and will repeat the analyses if necessary; however, EPA reviewed the data qualitatively, which is permitted given the use for which it is intended.

Dr. Philpott concluded that the Board recommends that EPA use caution regarding its reliance on the statistical analyses reported and to take this issue into account when considering how to use the data.

Ethical Considerations – Kisicki et al. (1999) Study

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

Dr. Menikoff noted that the prevailing standards at the time the study was conducted consisted of a version of the Common Rule and some FDA guidelines. The study was reviewed by the IRB at MDS-Harris and an ICF was signed. It appears that some screening procedures (urine collection and blood draws) took place before consent was obtained, but it is unclear whether the subjects had received information about the study at this time. The study was not fundamentally unethical because there is no evidence of intent to seriously harm the subjects and some form of informed consent was obtained. The study was designed to minimize harm.

To judge that the study deviated significantly from existing standards, there must be clear and convincing evidence that these deviations could have resulted in serious harm, based on knowledge available at the time, or that the deviations would have seriously impaired informed consent. There is no indication that such deviations occurred. Information about appropriate levels of risk was provided, and the study was designed to avoid administration of a harmful dose of chlorpyrifos. Collection of urine and blood samples before the ICF was signed was a deviation, but did not increase potential harm to the participants. Collecting urine and blood are not high-risk procedures and at this point, those involved likely knew they would be participating in the study. There is no evidence that this action impaired consent. He reminded the Board that the significance of the deviation, rather than the number of regulatory deviations, is what should be determined regarding EPA's ability to use the data.

Dr. Menikoff agreed that the ICF was not ideal and had numerous problems including a high readability level and confusion about possible adverse effects of participating; however, the ICF did list potential side effects (headache, dizziness, etc.). The ICF stated that no adverse effects were expected, but medical experts were on hand. The ICF was long (7 pages) and poorly written, but adequately conveyed the basic intent of the study—participants would receive a dose of pesticide that may, but probably would not, harm them. This was adequate to inform participants about the possible risks of the study. Again, there is no evidence that consent was seriously impaired and thus EPA can rely on this study.

Prof. Meisel stated that voluntary consent appeared to be compromised by the failure of the investigators to obtain informed consent before subjects entered the study; this could lead subjects to feel psychologically committed to participation before fully understanding the risks and benefits of participation and make them more reluctant to decline to participate or withdraw. The statement in the ICF noting that in the opinion of MDS-Harris medical consultants, the risks of participation are not significant, also undercuts the ICF. Prof. Meisel concluded that there was clear and convincing evidence that the study was unethical.

In response to a question from Dr. Popendorf, Prof. Meisel clarified that providing urine and blood collection before signing the consent form could have made the participants feel psychologically committed to participating in the study. Participating before full consent was

obtained undercuts the voluntary aspect of consent. Mr. Carley referred to the study report calendar that demonstrated that the time from which subjects were screened and blood and urine samples were obtained to the time at which they signed the ICF ranged from 1 day to 1 week. On June 24, 2009, EPA received a copy of a letter from MDS-Harris responding to Mr. Carley's questions on this matter. The letter states that the company used an internal standard operating procedure (SOP) for screening participants in this study. The subjects arrived at the research facility and received an information packet that contained the ICF. Before undergoing screening, they listened to a tape recording of the ICF and read along. A research associate was available for questions. The participants signed a document attesting that they had listened to the recording of the ICF, understood it, and had no further questions. The participants did not sign the ICF, but they did review and understand it. In light of this information, Prof. Meisel withdrew his comment. Dr. Philpott added that informed consent is a process in addition to a form. He commended MDS-Harris for providing this additional information.

Dr. Philpott agreed with Dr. Menikoff's and Prof. Meisel's conclusions regarding the ethics of this study. The Board consensus was that, although there were concerns about the study conduct with respect to the ICF and the informed consent process, there was no clear and convincing evidence that the study was unethical or significantly deficient according to the prevailing ethical standards.

Summary of Board Response to the Charge Questions

The Board provided a summary of their responses to the charge questions pertaining to the chlorpyrifos human toxicity studies, but cautioned that the responses were not final until review and approval of the final Board report for this meeting.

Nolan et al. (1982) Study

Regarding the reliability of the blood and urine measurements of chlorpyrifos and/or TCP in this study, the Board consensus was that the measurements of chlorpyrifos are at the limit of detection and are not useful. The measurement of TCP in urine is generally reliable, but the utility of the measurement of TCP in blood is unclear because of concerns about the detection of the appropriate TCP conjugate.

Regarding the reliability of the measurements of ChE activity/inhibition from the Nolan et al. oral and dermal studies, the plasma ChE studies are generally reliable, but there were concerns about the laboratory variability and lack of a control group. The Board also expressed concerns about RBC assay variability but the data appear to support the conclusion that there is no inhibition of RBC ChE.

Regarding the ethical conduct of the study, although concerned about the lack of a protocol to review, the Board concluded that there was no clear and convincing evidence that the study was fundamentally unethical or significantly deficient according to the standards of the time.

Honeycutt and DeGeare (1993) Study

Regarding the blood and urine measurements of chlorpyrifos and/or TCP from the Honeycutt and DeGeare worker biomonitoring study, the Board concluded that the data are likely reliable but of limited value because of the small sample size, background exposure was not accounted for, urine collection was incomplete, and high daily variation was observed.

Regarding the measurements of ChE activity/inhibition, the Board believed that the laboratory data are likely accurate and reliable but had concerns about its utility. Some of the Board's concerns included the lack of untreated controls, measuring only a single post-exposure time point, small sample size, and likely irreproducibility of the study.

Regarding ethical conduct of the study, the Board concluded that there was no clear and convincing evidence that the study was fundamentally unethical or significantly deficient according to the standards of the time, but had concerns about participants being influenced to participate and about confidentiality.

Kisicki et al. (1999) Study

Regarding the reliability of the blood and urine measurements of chlorpyrifos and/or TCP from the Kisicki et al. oral study, the Board had questions about the analytic procedures, lack of an appropriate glucuronide control, and discrepancies between the absorption data from this study compared to that reported in Nolan et al.; these issues raise concerns about the reliability and utility of these data for risk assessment purposes.

The Board concluded that the measurements of ChE activity/inhibition from the Kisicki et al. oral study were reliable, but cautioned EPA about the incomplete profile for the one responder at the highest dose level and about relying on the statistical analyses as presented in the report.

Although the Board had considerable concerns about the ICF and informed consent process, the Board concluded that there was no clear and convincing evidence that the study was fundamentally unethical or significantly deficient according to the standards of the time.

Review of February 17, 2009 HSRB Meeting Report

Dr. Lewis described the review process. The Board prepared a draft report that responded to EPA charge questions discussed during the February 2009 teleconference. The draft report was released for public comment; no public comments were received prior to this meeting. At this meeting, the Board conducts its final review of the report and will discuss any changes. At the end of the discussion, Dr. Philpott asks each Board member to approve the report. Dr. Philpott added that the Agency had no comments on this report.

Regarding the study SPC-001 by CLBR, which was a field test of picaridin-containing products against mosquitoes, the Board consensus was that the study provided scientifically valid results to assess the efficacy of this product. The Board recommended that EPA re-evaluate the

statistical analyses required for repellency testing and how to use the data to define specific protection times. The Board concluded that the study was conducted in substantial compliance with 40 CFR part 26, subparts K and L. The Board also reviewed the completed study SPC-002, conducted by CLBR, which was a laboratory test of the efficacy of picaridin products against ticks. The Board consensus was that the study was scientifically valid for assessing efficacy against ticks; however, the Board recommended that EPA reconsider how the data are used to inform specific protection times. The Board concluded that the study was conducted in substantial compliance with 40 CFR part 26, subparts K and L.

The Board was also asked by EPA to address specific questions related to spatial insect repellent testing protocols. The Board discussed points EPA should consider when drafting recommendations and guidelines that will be provided to sponsors. They concluded that environmental and human factors should be addressed. Study design should include standards for minimal allowable pest densities. EPA also should develop a statement of efficacy based on parameters such as numbers of insects knocked down, duration of insect exclusion, and so forth. EPA and sponsors should develop standard use protocols for devices used to dispense spatial repellents. With respect to sample size and statistics, the allocation of "units" (e.g., humans) and how to balance sample size relevant to other environmental aspects will be critical for determining sample size and analyses. Data censoring will bias results. Sponsors will need to define response variables and what will affect them. Before conducting spatial tests with humans as bait, the Board also must have sufficient information to determine that use of humans in these studies is scientifically justified and ethical.

Dr. Johnson clarified that the "experimental unit" is actually the area where the pesticide is applied (page 18, lines 40-43) and not the individual human subject. This should be clarified in the report and included in the cover letter to OPP because it is an important point for sample size determination and randomization. Dr. Philpott agreed to these changes.

Dr. Philpott asked each Board member to approve the changes to the report and cover letter. All members approved all changes.

Concluding Remarks

On behalf of EPA, Mr. Jordan thanked the Board for their efforts at this meeting. He explained that the Board received no comments from the Agency on its report for the February 17, 2009 meeting because the Agency found the new format to be clear and concise and had no disagreements or need for clarification. He commended the Board on the new format of the report.

Mr. Jordan also thanked the Board for their advice on the chlorpyrifos studies, noting that this advice was clear, constructive, thoughtful and helpful. The discussion was both interesting and helpful because the Board took care to explain how it assessed the information and reached conclusions about the reliability and accuracy of the data, how the data should be used, and caveats and limitations to its use. EPA appreciated this effort and also the contribution of members and consultants with different areas of expertise. Mr. Jordan thanked Board members for their diligence in reviewing the large amount of material provided for the chlorpyrifos studies

and their flexibility and patience regarding the changes made to the studies that would be reviewed and to the charge questions.

Thursday June 25, 2009 – Welcoming Remarks

Dr. Lewis opened the meeting and welcomed Board members, EPA staff, and the public. The day's agenda included review of two insect repellent protocols and a proposed AHETF scenario design and field study protocol to test exposure of workers mixing or loading wettable powder in water-soluble packaging. Mr. Carley added that the letter from MDS-Harris clarifying the consent procedure for the Kisicki et al. (1999) study will be made available at www.regulations.gov and on the HSRB portal for Board members.

Follow-up from Previous Day

Mr. Jordan declined to provide follow-up comments.

CLBR Protocol LNX-002: Efficacy of Picaridin-Based Personal Insect Repellents against Biting Flies in the Field

Background

Mr. Carley provided background information on LNX-002. This protocol was submitted by CLBR and proposes a field study of the repellent efficacy against biting flies of two conditionally registered formulations containing 20 percent picaridin. The initial submission, along with information from the IRB, meets the standard of completeness defined in 40 CFR §26.115 and is thus ready for HSRB review.

The protocol is similar to mosquito repellent field studies from CLBR previously reviewed by the Board. The test materials are the same as those tested by CLBR against mosquitoes in LNX-001. The LNX-002 protocol proposes to use the "typical consumer dose" determined in LNX-001.

In contrast to previous protocols, this is the first protocol to be reviewed by the HSRB that tests repellent efficacy against biting flies in the field. The protocol describes only 1 field trial, conducted in a single habitat. Subjects will be exposed for 5-minute periods every 30 minutes; previous protocols exposed subjects for 1 minute every 15 minutes. The protocol also has been newly formatted to incorporate previous EPA and HSRB comments. Mr. Carley commended Dr. Scott Carroll for his efforts, which streamlined the organization of the protocol, leading to improved clarity and a reduction in redundancy.

EPA Science Assessment: LNX-002

Mr. Kevin Sweeney (OPP, EPA) provided EPA's science assessment of LNX-002. The objectives of this study were to test the repellent efficacy of the test material against biting flies in the field and to satisfy a condition of registration. The test materials were EPA Registration Number 33967-50 (lotion) and 39967-53 (pump spray). Both products contain 20 percent

picaridin. The oral Lethal Dose 50 (LD-50) for these products is greater than 5,000 mg/kg and the dermal LD-50 is greater than 2,000 mg/kg.

Dose rates used were those established for the same test materials in LNX-001, which was reviewed by the Board in October 2008. Because lotion and spray treatments are easily distinguishable, the study will be only partially blinded; however, the technicians recording the results will not know which treatment was applied to which subject(s). Ten subjects will be treated with each formulation and 2 untreated control subjects will participate in a single field trial; untreated subjects will monitor biting fly pressure, but their data will not be used in the analyses of efficacy. Both treated and untreated subjects will be exposed to biting flies for 5 minutes of every 30 minutes. No positive or vehicle controls are proposed.

The study will be conducted at a field site in the California Central Valley. Expected biting fly populations include biting midges (*Leptoconops carteri*) or black flies (*Simulium cf. vittatum*). Measured variables include subject limb area, biting pressure (must be ≥ 1 landing with intent to bite (LIBe) in 5 minutes), first confirmed LIBe (FCLIBe), and time to FCLIBe. Presence of fly populations will be documented.

The duration of "complete protection time" (CPT) will be calculated as the mean time across all treated subjects from treatment to FCLIBe. CPT will be presented with standard deviation and 95 percent confidence interval. Untreated controls will not be used for comparison of treatment means. Other analyses, including Kaplan-Meier survivor analysis, will be conducted if appropriate.

MOEs were calculated for arms and legs for both the lotion and spray formulations. The MOEs for the lotion product are 547 for arms and 255 for legs. MOEs for the spray product are 1,386 for the arms and 70 for the legs. The target MOE for picaridin products is 100; thus these doses are within the safe range.

The sample size of 10 with 2 controls is justified as a compromise between financial and scientific concerns and is adequate to achieve statistically meaningful results. EPA guidelines recommend 6 replicates and EPA believes a sample size of 10 treated subjects is acceptable for a study of this type.

Some deficiencies were noted in EPA's review. The standard of biting pressure is not well justified; a standard of 1 LIBe in 5 minutes may not be high enough to ensure a valid test. The low standard may lead to few failures of the products and right-censored data. In addition, the shift from sampling for 1 minute in 15 minutes to 5 minutes in 30 minutes was not explained. If amended to address these concerns, the LNX-002 protocol is likely to yield scientifically reliable information. This information should satisfy the scientific criteria from the framework recommended by the HSRB, namely it would produce important information that cannot be obtained except from research with human subjects, it has clear scientific objectives, and the study design should produce data adequate to achieve those objectives.

Clarifying Questions

Dr. Young stated that to judge the reliability and adequacy of the study design, the study objective must be clear. She asked if this is the only study that will provide data EPA will use to determine the adequacy of protection provided by this product against biting flies. Mr. Sweeney responded that other data would be used in conjunction with these data to determine protection. He explained that the purpose of the study is to demonstrate whether the product repels flies under field conditions.

Dr. Young inquired if the substitution of species that might occur if certain species are not found at the field site was acceptable to EPA. Mr. Sweeney explained that although EPA understands that black flies, white flies, and midges are not identical, all fall under the category of "biting flies" and EPA allows several species to be used as representative of flies in this category; EPA does not require products to be tested against all species. Dr. Young noted that the aggressiveness of the species differed and this could affect repellency. Mr. Sweeney added that the field site was expected to harbor black flies and biting midges. EPA has data from a laboratory study that tested this product against stable flies; EPA is particularly interested in obtaining data on black flies. Dr. Young asked if any studies of the relative efficacy of the product against different species had been performed. Mr. Sweeney replied that there may be some information in literature published by the military. The *Journal of Medical Entomology* has an article describing the efficacy of different repellants against ticks and black flies in New York State. EPA also has some unpublished data on this topic.

Dr. Young stated that there is no evidence for how the hypothetical mean relates to the duration of the study. The CPT estimate and estimated study duration will affect the design of the study. Mr. Sweeney explained that repellency studies of this type usually last for 10 to 12 hours or until product failure. Dr. Johnson noted that previous similar studies involved 2 field sites and 10 subjects per site; he asked if EPA found testing at just 1 site with 10 subjects acceptable. Mr. Sweeney answered that EPA was satisfied with this design but a larger number of subjects also would be acceptable. He explained that it was questionable whether another suitable field site with these fly populations could be identified and EPA was not convinced that data from more sites was needed.

Dr. Chambers questioned if the guidelines calling for testing mosquito repellency at two sites but fly repellency at only one site was based on practical consideration. Mr. Sweeney confirmed that this was the case. Dr. Young asked why two sites were required for mosquito testing. Mr. Sweeney explained that two sites were required for mosquito testing because different species were found at different sites and in different types of habitats. Biting fly habitats tend to be similar across species.

<u>EPA Ethics Assessment: LNX-002</u>

Mr. Carley provided EPA's ethics review of LNX-002. The proposed study would test the repellent efficacy of two test formulations against biting flies in the field. Both products are conditionally registered; product-specific field efficacy testing is required to support label claims of repellency against biting flies. The work presents potential value to society because biting

flies can be serious nuisance pests and these products might represent potentially attractive alternatives to other available repellents.

Subjects will be recruited from people who have expressed interest in participating in repellency tests, supplemented by word of mouth; CLBR maintains a database of people (diverse for race and gender) who have previously participated in or expressed interest in participating in repellency studies. Inclusion and exclusion factors are well defined and appropriate. The study includes individuals between the ages of 18 and 55 years; the upper age limit was established to protect older people who are at increased risk from mosquito-borne diseases (mosquitoes likely will be present at the field test site). Participants also must speak and read English and understand the ICF. The study excluded pregnant and nursing women and students of the employer. People with sensitivity to the product, fly bites, or in poor physical condition were also excluded.

Risks to subjects included eye irritation on contact with the repellents; the repellents also are harmful if swallowed. Other risks include possible exposure to biting arthropods and arthropod-borne disease, physical stress of participation, and breach of privacy. Risk from biting flies was minimized by excluding subjects who are sensitive to fly bites and by training participants to remove the flies before they bite. Exposure to arthropod-borne disease was minimized by ensuring that no mosquito-borne diseases were present at the field site area for 2 weeks preceding the conduct of the study, aspirating insects before they can bite, and collecting insects to test for pathogens. Risks associated with physical stress caused by spending a long day in the field are minimized by excluding people in poor physical condition. Privacy is insured by proper record management and use of alternate subjects to avoid possible embarrassment from a positive pregnancy test.

The study offers no direct benefit to the subjects; the primary direct beneficiary is the sponsor. If the test materials are proven effective and remain on the market, indirect beneficiaries will include repellent users who prefer one of these products to other repellents. The investigator has taken all reasonable opportunities to further reduce risk, while maintaining scientific robustness. The probability of residual risks to subjects can be accurately characterized as "extremely small." The risks to subjects are reasonable given the expected societal benefits of the knowledge likely to be gained.

The Independent Investigational Review Board (IIRB) of Plantation, FL, has reviewed and approved the protocol and informed consent materials, is independent of the sponsors and investigators, is registered with OHRP, and is seeking accreditation from the Association for Accreditation of Human Research Participant Protection (AAHRPP). A "Human Research Protection Program Plan" from IIRB is included in the supplemental submission of IRB materials. The description of subject recruiting and consent processes is complete and satisfactory. Separate IRB-approved ICFs are provided for treated subjects and for untreated controls. ICFs include all elements required by regulations and are written at appropriate language and reading levels. The methods proposed for managing information about prospective and enrolled subjects will effectively protect their privacy. Subjects are free to withdraw at any time and will be reminded of this. The proposed level of compensation is appropriate and subjects who withdraw and alternate subjects who are not needed for the field trial will

be compensated. 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 data to EPA under the pesticide laws. The primary ethical standards applicable to the conduct of this research are 40 CFR part 26, subparts K and L. Attachment 1 to the EPA Review contains a point-by-point evaluation of how this protocol addresses the requirements of 40 CFR part 26, subparts K and L and additional criteria suggested by the HSRB. EPA found no deficiencies relative to 40 CFR part 26, subparts K and L or to FIFRA §12(a)(2)(P). EPA defers to reviewers in the CDPR to assess compliance with applicable California state requirements. One minor drafting error was noted in the protocol, and the discussion of stopping rules should be corrected.

The proposed research meets all requirements of §26.1111, §26.1116, §26.1117, §26.1125 and §26.1203. All elements of NAS recommendations 5-1 and 5-2 are satisfied. If further revised to correct the identified drafting error, CLBR protocol LNX-002 will meet the applicable requirements of 40 CFR part 26, subparts K and L.

Clarifying Questions

Prof. Meisel requested clarification of the reason to allow only those who had participated in previous studies to serve as untreated controls. Mr. Carley explained that those serving as untreated controls must have participated in previous studies and been trained in insect aspiration. Most untreated controls are graduate students who have been so trained and appreciate the risk of exposure to biting insects.

Clarifying Questions for Principal Investigator/Sponsor

Dr. Carroll, CLBR and Mr. Shawn King, CLBR

Dr. Carroll was asked to address Dr. Young's questions regarding substitution of different species at the test site, given differences in insect behaviors and aggressiveness. Dr. Carroll agreed that it would be ideal to have the specified species present at the field site; however, most repellent agents appear to be broad spectrum. The 1999 Agency guideline for the design of studies of repellency against biting flies stipulates testing against black flies, white flies, stable flies, deer flies and midges; these species are not closely related. There is little evidence regarding how these species find a host and how repellent agents influence their behavior. Dr. Carroll explained that he relies on industry precedence; over the long term, the repellents have shown sufficient broad-spectrum efficacy to be labeled as repelling biting flies in general. He conceded that the efficacy spectrum of picaridin was unknown, but it repels mosquitoes and midges and there is some data that indicates it repels biting flies on horses.

Dr. Johnson asked why substitution might be necessary. Dr. Carroll explained that ideally all species would be present at the field site; however, given the extensive protocol review process and the seasonality of the species, conduct of the field trial cannot be precisely scheduled. All the proposed fly species are of interest to the consumer, which warrants testing

against any of them. Dr. Johnson inquired how the results would be interpreted if black flies are not present at the time of the study. Dr. Carroll replied that, given the presence of other species, the study will nonetheless generate data to submit to EPA; he agreed that he was unlikely to generate data on all four species in this trial. Labeling decisions are made by EPA, but precedent suggests that testing against a single species is sufficient to judge efficacy against biting flies. In response to Dr. Lebowitz, Dr. Carroll explained that he will record the type of fly present to the best of his ability, although identification depends on the ability of the participants to catch the flies. Raw data will be provided to permit differentiation of species. It is fairly simple to distinguish among species and thus there will be a time course for each species. Dr. Chambers asked if, in the presence of more than one species, untreated controls will be monitored for all or only one species. Dr. Carroll answered that having a single species present at adequate landing pressure was the most likely scenario. If two species are present at adequate landing pressure, the intent is to monitor both simultaneously. He offered to clarify verbiage in the protocol to explain this possibility.

Dr. Philpott requested clarification of Dr. Young's questions regarding the estimated CPT and possible data censoring. Dr. Carroll answered that he based this determination on published literature describing the efficacy of the products against mosquitoes, which indicate CPTs of between 6 and 12 hours. He explained that difficulties arose when testing took place late in the year when the days were shorter and the new repellents that were being tested lasted longer than previous products. The 20 percent picaridin products are the most active products tested to date, with CPT against mosquitoes of 14 hours. This trial is planned for conduct near the summer solstice to ensure at least 12 hours of daylight. Most repellents tend to last for a shorter time for flies; 8 to 10 hours of protection are expected, based on information in the literature. Dr. Young asked if fly behavior changed depending on time of day. Dr. Carroll explained that the field site has sufficient humidity, shade, and lack of wind that should ensure flies will be at high levels throughout the day.

Dr. Carroll addressed Board concerns regarding the use of one field site rather than two. Dr. Carroll explained that habitat has less influence on the composition of biting fly communities than it does on mosquitoes. Fly species are not as diverse as mosquito species in the United States. A shift in habitat would not have a significant effect on the presence of different species within a given taxa. Use of the single site and testing based on a single species is adequate for labeling, based on the 1999 public draft of the EPA Repellent Test Guidelines.

Dr. Philpott asked Dr. Carroll to explain the difference in exposure intervals for treated versus untreated subjects. Dr. Carroll clarified that exposure intervals are the same for both groups. Dr. Philpott asked Dr. Carroll to address Prof. Meisel's questions concerning the definition of third-party coverage of medical costs. Dr. Carroll answered that 30 to 40 percent of the subjects are students who may be covered by their parent's health care. Thus, CLBR will cover the cost of medical care not covered by a subject's own or their parent's medical coverage.

Dr. Chambers inquired how participants would recognize intent to bite in flies. Dr. Carroll answered that the approach is similar to that used to prevent mosquito bites. Black flies and biting midges tend to walk about after landing and before biting; there is significant time to remove them before they bite.

Dr. Young asked if there was sufficient evidence to suggest that no interaction of the repellent would occur if the subjects stood too close together. Dr. Carroll answered that treated subjects will stand as far apart as is feasible to allow them to still observe one another. Although interaction is possible, the subjects all are testing the same active ingredient. There is some evidence of interaction between treated participants using spray products, but this interaction probably is not strong.

Dr. Philpott requested clarification of the switch from 1 month of no arbovirus activity at the test site to only 2 weeks. Dr. Carroll answered that when drafting the first of these protocols, CDPR raised concerns about minimizing risk in as many ways as possible. At this time, Dr. Carroll did not feel sufficiently comfortable with his knowledge of arbovirus presence and activity to determine risk of exposure to use a smaller arbovirus-free period. Since then, more knowledge has been gained about the test sites and surveillance workers have not detected pathogens at the sites in 20 years. Using the 1-month window severely truncated the study season. As he grew more comfortable with the arbovirus data and the site, Dr. Carroll decided that a 2-week window would sufficiently mitigate risk.

Dr. Popendorf questioned whether the chemical was volatile and how it loses its effectiveness. Dr. Carroll answered that loss of effectiveness occurs through evaporation and absorption. Picaridin does not absorb as quickly as DEET and also evaporates more slowly, leading to long protection times. To be effective against mosquitoes, some evaporation must occur, creating a concentration of volatile compounds near the skin surface. The area of protection of picaridin is probably about half a meter. Oil of lemon eucalyptus lasts longer but is highly evaporative, creating an area of approximately 10 meters; testing this product requires untreated participants to stay much farther away from treated participants. Dr. Popendorf asked if subjects stand at least 1 meter (m) apart. Dr. Carroll answered that subjects maintain a feet-to-feet separation of 75 centimeters (cm), with knees over 1 m apart.

Dr. Carroll had no further statements or clarifications related to the EPA presentation.

Public Comments

Dr. Philpott invited oral public comment on the proposed field repellency study protocol LNX-002. No oral public comments were presented.

Board Discussion

Dr. Lewis explained that the purpose of the Board discussion of LNX-002 is to provide a response to the EPA charge questions; this response will be finalized in the Board report. He reiterated his remarks about consultants from the previous day that they provide expertise to the Board to assist with the review, but are not part of the deliberative process; however, consultants were assigned as associate discussants for this meeting.

Scientific Considerations – LNX-002

Dr. Chambers stated that the research generated by the protocol LNX-002 is likely to generate scientifically reliable and useful data for assessing the efficacy of the tested materials in repelling biting flies in the field. She commended Dr. Carroll on his responsiveness to Board questions and complimented the improved clarity of his protocol. This protocol was exceptionally clear and incorporated Board input well. Dr. Carroll continues to use LIBe rather than bites to minimize subject risk and his use of 10 subjects is more than that called for by EPA guidelines; therefore, data useful for the protocol's intended purpose should be generated.

Dr. Young stated that the protocol needed to be revised, given that available data on biting flies shows that different species display different behaviors; therefore, allowing substitutions of species is not suitable. Black flies should be required to be at the site because these flies tend to be more aggressive. Dr. Young appreciated the comprehensiveness of the protection time calculation; however, she noted that a biting pressure of 1 bite per 5 minutes might, given a typical distribution, lead to a 95 percent probability of a 3.5-hour protection time. She recommended that the required biting pressure be increased. She added that the protocol did not present adequate plans for handling censored data; at least a portion of the subjects must experience product failure for the planned analyses to be correct. Dr. Young performed simulations and found that if 3 out of 10 subjects experience failure, a broad confidence interval will be generated. If EPA wants data to determine CPT, longer studies are needed for accuracy. She agreed that although a sample size of 10 subjects appears small, this is consistent with previous studies and will be satisfactory if similar protection times are realized.

Dr. Lianne Sheppard, an HSRB consultant, questioned whether the short duration of exposure was typical of these studies, given that in real use, people do not enter a protected shelter. Dr. Young explained that mean protection time is relative to the length of the study.

Dr. Lehman-Mckeeman stated that Dr. Carroll's justification to use different species found in the field was compelling. Dr. Chambers concluded that the naming of specific species in the protocol does not constitute a mandate; Dr. Lehman-Mckeeman concurred with this conclusion. Given Dr. Carroll's explanations regarding insect behavior and the efficacy of typical insect repellents against different species, the presence of any of the species should be adequate. Dr. Lebowitz agreed with Dr. Lehman-Mckeeman that the exact species present was not a significant concern. Previous work would have detected significant differences in insect behavior. Dr. Chambers agreed that Dr. Carroll has adequate knowledge regarding insects and insect repellent products to judge the need for different species. Requiring specific flies to be present during conduct of the study could result in the entire study being cancelled. Dr. Young stated that her main concern was that black flies, in her experience, are different than stable flies. There are no data stating that the flies are different, but there are no data concluding that their behaviors are the same. If the data are to be used for labeling purposes, data on other species are needed. She reiterated that, in her experience, black flies are more aggressive and thus these or other aggressive species need to be present during testing.

Dr. Philpott summarized that the Board had some concerns about study design and recommended some revisions before study implementation. He also noted the concerns of some

Board members regarding choice of species. Dr. Carroll indicated that he will amend the protocol if there is a change in biting pressure of certain species during conduct of the study. There was disagreement among Board members regarding which species should be present at the test site. Some members agree with EPA guidelines that the presence of any one biting fly species is adequate, while others contend that there is inadequate justification for substitution of species, particularly given that these data will be used for labeling purposes. The Board could recommend that EPA seek greater clarification and justification for species selection and substitution.

Dr. Johnson stated that he did not have a strong opinion regarding substitution of horse flies for stable flies to judge product efficacy; however, black flies and midges appear to have different behavior. He suggested that the Board recommend that sufficient biting pressure from black flies or midges be present at the test site for the study to proceed. Sufficient biting pressure for either of the two species would be sufficient for EPA to use the data for label claims.

Dr. Lebowitz recommended that the 5-minute exposure in 30 minutes design be clarified because it will affect data censoring. Dr. Popendorf added that the way biting pressure could affect CPT was unclear. Dr. Philpott explained that, by chance, the stipulated biting pressure could result in a 3.5-hour protection time; therefore, clarification is needed regarding whether 1 bite every 5 minutes is sufficient. He asked if the Board needed to review this protocol again after the changes discussed during this meeting were made, or if EPA could decide that the changes were sufficient. Drs. Lebowitz and Young responded that the Board did not need to review the protocol again.

Dr. Chambers argued that this conclusion was significantly different from her conclusion that any of the four species could be present. Requiring the presence of at least two species unnecessarily restricts the investigator's ability to conduct the trial. Dr. Lebowitz suggested that the Board consensus state that there was concern about the presence of sufficient numbers and types of species. Dr. Philpott inquired if a statement that a lack of certain species (black flies and midges) could compromise review of the completed trial. Dr. Chambers disagreed with the implication that the study could be rejected if specific species were not present during its conduct. Dr. Young noted that Mr. Sweeney had stated that EPA already has data on stable flies and does not need more such data. Because EPA already has stable fly data and because horse flies are similar to stable flies, she countered that either black flies or midges must be present at sufficient biting pressure to conduct the trial. Dr. Chambers asked if EPA labeling practice is currently based on data generated for all species; she was concerned that labels be kept consistent for the consumer. Mr. Jordan explained that EPA's approach to labeling is to balance information to the consumer with accurate representation of all available information. When creating labels describing efficacy of topical repellents against biting flies, EPA has not identified each species; the label states that the product is effective against "biting flies." The data EPA has appears to support the contention that the products are equally effective against all fly species. It also is appropriate to label a product as effective against "biting flies" because most consumers cannot distinguish between fly species. Because available data suggest comparable effectiveness, EPA has historically accepted label claims supported by data against any one of the four species identified in the LNX-002 protocol. It would be preferable to have data on multiple species, but this has not historically been required. The Agency would inform

Dr. Carroll that it was important to try to ensure that the study was conducted at a site with species other than stable flies (e.g., black flies and midges).

Dr. Lebowitz suggested that the Board emphasize in its recommendations that either black flies or midges be present. This would concur with the strong desire of EPA to have Dr. Carroll conduct the trial at a site where these species are present. Dr. Philpott summarized that the majority of the Board agreed with the recommendation that the study be conducted at a site and time at which there is sufficient biting pressure of black flies and midges. He noted that some Board members had concerns about this recommendation. He also recommended that Dr. Carroll clarify the reason for using an exposure time of 5 minutes every 30 minutes and whether this will be sufficient. He also should determine if the stipulated biting pressure is sufficient; Dr. Young has determined that at this biting pressure, a CPT of 3.5 hours could occur by chance. The protocol should clarify use of mean protection time versus duration of the study when analyzing the data. The protocol also should be clarified to allow measurement of either black flies or midges, and Dr. Carroll should attempt to identify the different flies present the site. Dr. Young clarified that the protocol should be revised so that the analyses can accommodate data censoring, for example, using Kaplan-Meier analysis or maximum likelihood methods. Dr. Philpott concluded that the Board is confident that Dr. Carroll and EPA will make these changes and the protocol does not need to be reviewed by the Board before execution.

Ethical Considerations – LNX-002

Dr. Philpott commended Mr. Carley on his review of the ethics of this protocol and concurred with his opinion regarding its strengths and weaknesses. He expressed some concern about potential exposure to arboviruses in mosquitoes present at the field site. This concern arose from the change in arbovirus monitoring from 1 month to 2 weeks, but given Dr. Carroll's explanation of this change, the plan to collect and analyze mosquitoes at the test site, and subject follow-up and monitoring, minimization of risks of mosquito-borne disease is adequate. He noted that the participants were not members of vulnerable populations and that mechanisms were in place to minimize possible undue influence, given Dr. Carroll's professional relationship with the University of California-Davis. Dr. Philpott concluded that the protocol met the pertinent ethical requirements.

Prof. Meisel agreed with Mr. Carley's ethics assessment. He expressed concern about the definition of third-party coverage of medical costs; given the interpretation provided by Dr. Carroll, this may refer to students' parents' insurance. The protocol should be revised to stipulate coverage of medical costs not covered by the participants' own insurance or by a third party that covers the participant.

Dr. Philpott summarized that the Board consensus was that, given the changes noted by Mr. Carley and Prof. Meisel regarding clarification of the ICF, the Board judged the protocol to be ethical.

Summary of Board Response to the Charge Questions

Is the research likely to generate scientifically reliable data, useful for assessing the efficacy of the tested materials in repelling biting flies in the field?

To ensure the likelihood that the study will obtain scientifically reliable data, the Board recommends significant changes to the protocol. The revised protocol, however, does not need to come before the Board for review prior to study execution.

The study should be conducted at a site and time with sufficient biting pressure of black flies and/or biting midges. The protocol must be modified to consider how to accurately measure one or both species. The choice of a 5 minute every 30 minute exposure interval should be clarified, particularly as it raises questions about sufficient biting pressure and the probability of erroneous CPT results. Mean protection times versus duration of the study should be clarified as this affects the prevalence of censored data. The protocol needs to be revised to clarify how the analysis will proceed in the presence of censored data (maximum-likelihood or Kaplan-Meier analyses).

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

If revised in accordance with the Agency's recommendations, along with a clarification of "3rd party" medical coverage, the study will likely meet the applicable requirements.

ICR, Inc. Study A382: Efficacy of Picaridin-Based Personal Insect Repellents Against Stable Flies in the Laboratory

Background

ICR, Inc. completed protocol A382, which is similar to an earlier ICR cage study that tested repellency against mosquitoes. However, A382 tested efficacy against stable flies. The endpoint was changed to first bite without confirmation to minimize subject risk, standards for aggressiveness/attractiveness differ because of differences between biting flies and mosquitoes, and the study includes a preliminary dose-determination phase. The test repellents are the same 20 percent picaridin lotion and pump spray products tested in protocol LNX-001.

The same test cage was used for this protocol as the protocol that tested efficacy against mosquitoes. The mesh cage has cloth sleeves through which participants place their arms, a wooden support for resting arms, and a mirrored floor for detecting flies on the underside of arms. The cages permit simultaneous testing of two subjects.

Protocol A382 was reviewed favorably by the Board in April 2008. ICR revised the protocol to reflect EPA and HSRB comments. The revised protocol was approved by the Essex Institutional Review Board (EIRB) on September 2, 2008. After further revision, EIRB approved the protocol on November 24, 2008. The dose determination phase of the protocol took place on September 18, 2008, under the version of the protocol approved on September 2,

2008. The dose determination was completed on October 2, 2008. Repellency testing was attempted on October 7, 2008 but was unsuccessful because the flies were insufficiently aggressive. ICR changed husbandry practices to improve aggressiveness. Repellency testing was successfully executed on December 9, 2008.

An informal submission of the study report was made to EPA on April 3, 2009. ICR was notified of gaps in ethics documentation on April 9, 2009. The formal study was submitted to EPA by Lanxess on April 23, 2009 and the supplemental ethics documentation was formally submitted by Lanxess on April 27, 2009.

EPA Science Assessment: ICR A382

Mr. Sweeney presented EPA's science assessment of protocol A382. The objectives of this study were to test the repellent efficacy of the test materials against caged stable flies in the laboratory, determine a typical consumer dose of the lotion and pump spray products, and satisfy a condition of registration. The test materials were EPA Registration Numbers 39967-50 (lotion) and 39967-53 (pump spray). Both products contain 20 percent picaridin. The oral LD-50 is greater than 5,000 mg/kg and the dermal LD-50 is greater than 2,000 mg/kg. Elements considered in EPA's science review included dose determination, MOE, study design, efficacy and conclusions drawn.

For the dose determination phase, 13 subjects self-dosed each test material to a 250 square cm (cm^2) area of the forearm. Dose measurement was determined by assessing the weight change of the container for the lotion and the weight change of a 50 cm^2 tape dosimeter on the arm for the spray product. This was repeated 3 times for each test material and the grand mean of subject means was used for the efficacy trial. Dose determination results were 0.87 g/250 cm^2 (grand mean dose) and 3.551microliters per cm^2 ($\mu l/cm^2$) (volumetric dose) for the lotion and 0.99 g/cm^2 (grand mean dose) and 4.125 $\mu l/cm^2$ (volumetric dose) for the pump spray. The MOE was calculated to be 376.

The repellent study design involved 12 subjects (7 males and 5 females). One negative control was used to establish the aggressiveness of the stable flies. Spray was applied to 1 arm and lotion to the other; treatments were randomized. Staff who recorded the results were blinded to treatments. The stable flies used were laboratory-reared *Stomoxys calcitrans L*. Each cage held 50 adult flies. Two subjects used each cage (total of 6 cages) and the arms of each subject were exposed for 5 minutes every 30 minutes for up to 10 hours or until product failure. The endpoint used was Time to First Bite.

Repellency testing generated a mean CPT of 4.5 ± 2.0 (2.5-6.5) hours and a median CPT of 5.5 hours for the lotion product. Mean CPT for the spray was 6.3 hours ± 2.0 (4.3-8.3) and median CPT was 6.5 hours. Only 2 of the subjects experienced product failure. EPA has concluded that this study was scientifically sound and that the data can be used to assess the repellency of the tested products against stable flies in the laboratory.

Clarifying Questions

Dr. Sheppard noted that although the repellency results table indicates a maximum of 8.3 hours of protection, 2 of the data points were censored at 10 hours. Mr. Carley clarified that this was due to a mistake made in drafting the slides for the presentation. Dr. Sidney Green, an HSRB consultant, asked about the utility of calculating the median for determining protection time, given the difference between the mean and median of the lotion. He asked if this was significant and how the median was used to evaluate CPT. Mr. Sweeney answered that EPA generally relies on mean CPT for labeling; the median was reported for the Kaplan-Meier analysis. Because the difference between median and mean was small, EPA considers the mean to be more reliable.

EPA Ethics Assessment: ICR A382

Mr. Carley presented EPA's ethics review of protocol A382. The documents considered in this assessment were the primary study report, ICR's supplemental submission, EPA's science and ethics review of the protocol (dated March 7, 2008), and the HSRB report from the April 2008 HSRB meeting (finalized on June 25, 2008). The primary study report MRID 47732701 inadequately documented the ethical conduct of the research, but most of these deficiencies were satisfactorily addressed in the supplemental submission MRID 47734901. Remaining deficiencies include documentation of EIRB member experience and expected contributions, documentation of fulfillment of promises of signature pages (the documents were received electronically but signature pages were not provided), and lack of evidence of substantive discussion of the proposal and amendments by EIRB.

In response to EPA's ethics review of March 7, 2008, a new section titled "Balance of Risks and Benefits" was added to the protocol. This section claimed that the potential risks of product safety, disease transmission, and bite irritation were minimal; thus, the benefit of potentially providing two effective stable fly repellent products offsets these minor risks. The HSRB asked for justification of exclusion of subjects older than 70 years of age. The new protocol cites an expected 10-hour study duration that could be tiring for older people. In response to a request for clarification regarding how subjects will be assessed for the ability to read, speak, and understand English, or why reading English is required, the new protocol includes an explanation that reading is needed for the informed consent process; however, the protocol does not address methods for assessing reading abilities. The Board also criticized the lack of plans for ensuring a racially diverse sample. The new protocol included promises to recruit and select minorities and to advertise if word-of-mouth is insufficient; the actual sample contained minorities. The HSRB also expressed concern about the blanket requirement for pregnancy testing, even of post-menopausal or surgically sterile women. The protocol was revised on November 10, 2008 to provide for a signed statement in lieu of pregnancy testing. The HSRB also questioned whether flies would be fed a bovine blood meal before use. The amended protocols assured the flies would receive no blood meals; however, this may have resulted in reduced aggressiveness of the flies used in the first implementation of the protocol. The investigators also ensured that ICR staff members assessing outcomes were blinded by having different staff apply treatments. Treatments also were randomized to left or right arms.

The applicable ethical standards were 40 CFR §26.1303, which requires documentation of the ethical conduct of the research; 40 CFR §26.1703, which forbids EPA to rely on data from research involving intentional exposure of pregnant or nursing women or of children; and 40 CFR §26.1705, which forbids EPA to rely on data from research initiated after April 6, 2006 unless there is adequate information to conclude that the research was conducted in substantial compliance with subparts A through L. FIFRA §12(a)(2)(P), which defines as testing any pesticides in humans unless they are fully informed and freely volunteer to participate as unlawful, also applies. With the supplemental submission of April 27, 2008, the requirements of 40 CFR §26.1303 were addressed sufficiently to support a thorough review. This protocol did not involve intentional exposure of pregnant or nursing women or of children younger than 18 years of age. No deviations from the protocol were reported. The investigators made an effort to address EPA and HSRB comments, although these efforts were not uniformly effective.

EPA has concluded that the conduct of this research was substantially consistent with the protocol as amended and approved by EIRB. None of the shortcomings in the ICR responses to EPA and HSRB comments adversely affected the rights or safety of the subjects or compromised the informed consent process. The overall record shows that the investigators prepared for and conducted protocol A382 in substantial compliance with 40 CRF part 26, subparts A through L. EPA finds no barriers in law or regulation to the Agency's reliance on A382 in its actions under FIFRA or §408 of FFDCA.

Clarifying Questions

Dr. Green noted that EPA claimed that EIRB had not provided sufficient information to allow the Agency to determine the contributions of each member of EIRB and that this was not the first time that this IRB did not comply with Agency requirements. He also noted that at the last meeting of EIRB, only two members and three alternates were present. EPA has concluded that none of this interfered with the ethical conduct of the study, which is probably true, but raises concerns about the seriousness with which EIRB views its role in this effort. He asked whether EPA continued to be willing to accept these deficiencies. Mr. Carley agreed that EPA has had concerns regarding the ability of EIRB to perform a thoughtful and thorough review. The Common Rule calls for identification of IRB members' experience and contributions; these are standard documentation requirements; however, with respect to compliance, the rules EPA applies pertain to the protocol submitters, not to the IRB. EPA has no direct contact with EIRB; the Agency is only provided with IRB documentation that is attached to the protocol reviews. By repeatedly noting concerns, EPA hopes that the accumulation of these concerns prompt EIRB to be more thorough in their reviews, or prompt their clients to seek another IRB. Mr. Carley explained that there are mechanisms to address IRB conduct when EPA has serious concerns. Dr. Warren Lux can enforce proper IRB conduct and has invoked this ability in the past. EPA hopes to continue to work with deficient IRBs directly to help them master the special concerns and issues surrounding review of repellency work.

Clarifying Questions for Principal Investigators

Dr. William Gaynor, ICR and Dr. Ralph Piedmont, Loyola College

Dr. Sheppard raised questions regarding proper calculation of the reported standard deviations, which appears to have been based on estimates of standard deviation from Kaplan-Meier analysis. Dr. Piedmont explained that at the time the study was developed, concerns about power and consistency of conclusions with previous estimates were a concern. Information in publications by Rutledge and Gupta were used to estimate power and the types of conclusions that could be drawn. Based on this, use of 12 subjects allowed estimation of a CPT of 8 hours ± 2 hours. The results indicated a protection time of less than 8 hours; therefore, protection time was calculated as 5.5 hours ± 2 hours. The actual standard deviation calculations are provided in the study report. Dr. Sheppard noted that the actual standard deviations are smaller than the estimated values, and thus the range is smaller. Power calculations are estimates and it is inappropriate to use these when reporting results. Dr. Piedmont offered to remove these values from the report.

Dr. Johnson referred to Table 4 of the submission, which reports protection time results for each subject. He noted that a protection time of only 1 hour was reported for 1 subject and asked if this meant the test product failed at 1 hour or at 1.5 hours. Dr. Piedmont answered that protection times were reported precisely and failure at 1 hour was reported as failure at 1 hour.

Dr. Sheppard questioned the significant variability in doses applied by the subjects and asked if dose were related to efficacy. Dr. Gaynor agreed that the doses were variable, which was expected based on what is known about human behavior. He speculated that a larger dose would provide a longer protection time. Dr. Sheppard asked if any efforts were made to determine the effect of application rates on efficacy. Dr. Gaynor explained that he did not know of any such studies, and clarified that each subject received the same amount of repellent in the testing phase, based on the results from the dosimetry phase. Dr. Sheppard questioned if there was a significant lag between the time repellent was provided to the first subject and the time testing began. Dr. Gaynor responded that there was less than a few minutes' difference. Dr. Sheppard requested clarification of how repellency was defined. Dr. Gaynor replied that only bites were counted as efficacy failure; landings were not considered failure. Dr. Sheppard asked if the protocol tested efficacy against landing or against biting. Dr. Gaynor agreed that a landing might indicate that the product was not repelling, but landing was probably less important to consumers than biting. Previously, investigators were required to observe a second confirming bite to define product breakdown. Dr. Sheppard noted that because no untreated subjects were tested, it is not possible to estimate the difference between treated versus untreated subjects. She asked whether this type of study truly answered the efficacy question. She also noted changes in the data collection sheets and asked why these changes were made. Dr. Gaynor answered that changes were probably due to entering data in the wrong column on the sheet; ICR has SOPs for making corrections.

Dr. Johnson said that the statement, "up to X hours of protection" seemed vague and suggested changing the wording to "at least X hours of protection." Dr. Piedmont explained that

the phrase "up to X hours of protection" referred to the power calculations. The data was reported as a distinct protection time with a standard deviation and confidence interval.

Clarifying Questions for the Study Sponsor

Dr. Ghona Sangha, Consultant to Lanxess Corporation

Dr. Sheppard asked how the results of this study would be used by EPA. Dr. Sangha explained that EPA will use the data to make product labeling decisions regarding protection time.

Dr. Green asked whether the sponsor of the research routinely examines the experience and performance of the IRBs used to review studies and if so, whether this sponsor was aware of EIRB deficiencies. Dr. Sangha answered that this was the first time this sponsor used EIRB and trusted them as an experienced IRB.

Public Comment

Dr. Sangha, Consultant to Lanxess Corporation

Dr. Sangha clarified that four species were included in the protocol submitted by Dr. Carroll because the laboratory study of this product used the same species for the first test; the lack of a blood meal might have resulted in insufficiently aggressive flies and thus new methodologies were needed to increase the number of flies present. This was the reason that stable flies were added to the field test protocol. The sponsor also recognizes the differences in aggressiveness across different species and thus added the four species to try to generate more reliable data.

Board Discussion

Scientific Considerations – A382

Dr. Chambers opened the discussion by stating that the study appears to be scientifically sound and was modified according to Board opinions voiced over the past few years. This group has not previously performed a dosimetry phase; given the wide range of variation in the amount of repellent applied by each subject, EPA should consider requiring a dosimetry phase for all of these types of studies. She commended ICR on responding to the Board's concerns about risk and using first bite rather than first confirmed bite as evidence of efficacy failure. She also commended ICR's responsiveness to the racial diversity issues raised by the Board. The MOEs are within a safe range. She concluded that the study provided sound data and the investigators had been responsive to EPA and Board concerns.

Dr. Sheppard asked that the investigators ensure that the treatment dose is clearly stated in the study; this was clear in EPA's review, but less clear in the report regarding whether grand mean or subject mean was used to defined dose. The statistical analyses are appropriate, but the conclusions should be revised to reflect that the confidence intervals were based on the estimated

standard error. Error estimates must be estimated from the data and not from the power calculations done before conducting the study. It also would be helpful if the investigators reported the observed range of protection times.

Regarding study design, Dr. Sheppard stated that it would have been preferable to use data from fly studies, rather than mosquito studies, to determine sample size. She disagreed that the lack of correlation between mean and standard deviation precluded use of fly data. Dr. Sheppard added that the data could be more thoroughly understood, for example, by including data on repellency and variance, a histogram of results, and any data showing whether, on a single subject, cream or spray product was associated with a longer protection time.

Dr. Green agreed with Dr. Chambers' assessment of the study. The data are sound from a scientific perspective. Dr. Sheppard's comments also should be taken into account. Dr. Chambers added that the table showing protection time for individuals is confusing and that Table 4 should indicate product failure time rather than protection time.

Dr. Philpott summarized that the Board found the study to be sufficiently scientifically sound for EPA to use the data to assess product efficacy against flies in the laboratory. The Board recommends that the analyses in which sample size calculations were used, rather than actual data, be removed from the final analysis, per Dr. Sheppard's comments.

Ethical Considerations – A382

Dr. Philpott agreed with Mr. Carley's assessment of the ethics of this protocol. He agreed that IRB conduct and quality is outside of EPA's authority, but expressed concern regarding the reviews performed by EIRB and their inability or refusal to provide complete information as requested. He recommended that the sponsors consider working with their IRBs to address gaps in information such as member qualifications and access to expert consultants.

The deficiencies noted by Mr. Carley, such as discrepancies between telephone scripts and recruitment materials are worthy of mention but did not affect the ethical conduct of the study, increase risk to participants, or impair the informed consent process. He commended the investigators on increasing participation of minorities and on their responsiveness to other Board concerns. Dr. Philpott specifically mentioned the investigators' willingness to use flies that had not received a blood meal, as this might have decreased fly aggressiveness. Given the available information, Dr. Philpott concluded that the protocol was conducted in substantial compliance with 40 CFR part 26, subparts K and L.

Prof. Meisel agreed with Dr. Philpott's conclusions. He also agreed that the qualifications of IRB members appeared inadequate and that information on these qualifications was difficult to obtain.

Dr. Philpott summarized that the Board judged the study to have been conducted in substantial compliance with the relevant regulations.

Summary of Board Response to the Charge Questions

Is the ICR study A382 sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy of the tested formulations against stable flies in the laboratory?

The Board concluded that the data were sufficiently sound to assess repellent efficacy against stable flies in the laboratory but raised concerns about data analysis and presentation, such as incorporating the assumed standard error estimate from the power and sample size calculation into the results.

Does available information support a determination that study A382 was conducted in substantial compliance with subparts K and L 40 CFR part 26?

The Board concluded that the study was conducted in substantial compliance with the appropriate subparts of 40 CFR part 26, although several Board members raised concerns about the quality of IRB review and the qualifications of IRB members.

AHETF Scenario Design and Field Study Protocol: Mixing/Loading Wettable Powder in Water Soluble Packaging

Background

Mr. Carley reviewed the structure of the AHETF monitoring program. The AHETF is a consortium of pesticide manufacturers who are seeking to develop new data for agricultural handler exposure to pesticides used during normal work activities. The Task Force has previously provided SOPs; SOPs that have been changed were provided to the Board in their background information.

A handler is defined as a worker who mixes, loads or applies pesticides. Scenarios, which describe handler activities and the settings in which they are performed, are defined by the Task Force in consultation with EPA and its sister groups in California and Canada. The sampling design is purposive but incorporates random sampling when feasible. The data generated are intended to help develop models of future exposures for works under specific conditions. EPA and AHETF are mindful of the desirability of the random sample design, but have concluded that the purposive design is likely to be more efficient and will generate data that will meet EPA's needs.

Each scenario has 5 clusters, which are monitoring sites located in different states. Growers are not part of the statistical design, but must be included in the program structure. To produce useable data, pesticides must be applied consistent with registered use and must be applied to crops; therefore, growers must be identified. After growers agree to participate, monitoring units (MUs) are chosen. An MU can be the grower himself or an employee of the grower. Each MU represents a set of data from 1 episode of monitoring 1 worker/handler. No more than 1 worker per grower will be monitored, for a total of 5 MUs in each of 5 clusters (25 MUs).

Dr. Philpott reminded the Board of previous discussions regarding sample design. The Board deemed a random sampling design to be preferable, but recognizes that this is not always possible. Purposive sampling was accepted, as long as a well-developed sampling frame is used. He asked Board members not to debate the merits of random versus purposive sampling during their deliberations. The Board should focus on determining whether incorporation of random elements is adequate.

Introduction

Ms. Kelly Sherman (OPP, EPA) introduced the AHETF protocol. The HSRB reviewed the closed-cab airblast scenario in June 2008. The AHETF conducted 2 closed-cab airblast field studies in the fall 2008. In October 2008, the HSRB reviewed the remaining field study protocols for the closed-cab airblast scenario and reviewed the scenario design document and field study protocols for the open-cab airblast scenario. The AHETF plans to conduct several closed-cab and open-cab airblast field studies in summer 2009.

No changes have been made to the AHETF Governing Document or most SOPs. The design objectives, sample size and rationale, and cluster configuration are all similar to other AHETF scenarios reviewed. Protocol procedures related to ethical conduct are similar, but all issues raised by EPA and the HSRB have been addressed.

Because this scenario monitors mixers and loaders rather than applicators, the crop type is unimportant. The scenario covers mixing dry pesticides in water-soluble packets (WSPs) with water and loading the solution into various types of equipment for application as liquid sprays. Liquid sprays may be applied to nearly all types of crops, using a wider range of application equipment in all areas of the United States. This proposal represents a new format for AHETF in that a single protocol covers all 5 proposed field study sites. There are 12 new or updated SOPs and one new surrogate (acephate).

EPA Science Assessment: AHE120

Mr. Jeff Evans (OPP, EPA) gave EPA's science assessment of the proposed protocol. The scenario for this protocol involves mixing or loading soluble or wettable powder pesticides enclosed in WSPs. EPA considers WSPs to be an engineering control to reduce inhalation exposure of dusty pesticides. The scenario supports assessing WSP mixing/loading for many crops under three sub-scenarios: (1) mixing of WSPs directly into the tank used for the pesticide application; (2) mixing of WSPs into a "pre-mix" tank at the same concentration to be applied to the crop; and (3) mixing of WSPs into a tank as a concentrated solution/suspension that must be further diluted and transferred to the final application tank. Many kinds of tanks are used; tanks may be located indoors or outdoors, and portable mixing stations may be used. These mixing and loading methods accompany a variety of applications scenarios.

EPA agrees with the AHETF plan to informally diversify these general equipment types; however, each of the three sub-scenarios must be monitored at least once within each cluster. Diversity will be achieved (randomly or purposively) by assigning mixer/loaders to

Amount-active-ingredient-Handled (AaiH) strata within each cluster. The AHETF proposes 25 subjects in 5 clusters of 5 subjects each as appropriate for this scenario.

The minimum personal protective equipment (PPE) permitted by the Worker Protection Standard for acephate and carbaryl when WSPs are used is chemical-resistant gloves. Other attire includes long-sleeved shirt, long pants, shoes and socks. In case of an emergency (e.g., bag rupture), other PPE (including coveralls, chemical-resistant footwear, and respirators) must be available. Inner dosimeters will be used to detect exposure.

Carbaryl has been previously used by the AHETF in its monitoring program; carbaryl has excellent recovery and analysis. Acephate has been used in worker exposure studies of applications in restaurants and homes. EPA accepts the AHETF's selection of acephate and carbaryl as surrogates because they are widely used and available in WSPs; are used on a wider range of crops on farms of many sizes and types such that all AaiH strata can be fulfilled within each cluster; have reliable analytical methods; have been successfully used as surrogates in other AHETF studies; and are known to have the required stability under field study conditions.

Maximum AaiHs are 720 lbs for acephate and 2,000 lbs for carbaryl; these amounts are sufficient to fulfill the upper end of the AaiH strata. Dermal MOEs are 858 for acephate and 531 for carbyl. Inhalation MOEs are 113 for acephate and 160 for carbaryl. Combined MOEs are 100 for acephate and 123 for carbaryl. Within each proposed AaiH strata, all exposure durations will be at least 4 hours and each subject will mix/load at least 3 tanks of spray. The 5 strata of each AaiH are 5 to 17 lbs AaiH, 18 to 55 lbs AaiH, 56 to 182 lbs AaiH, 183 to 603 lbs AaiH, and 604 to 2,000 lbs (use of acephate is limited to 700 lbs) AaiH.

The proposed clusters are located in five different states. These include New York, with a cool climate and orchard/trellis crop types; Louisiana, with a hot/humid climate and field crops (cotton, soybean); Michigan, with a cool climate and orchard/trellis vegetables; southern California, with a hot/dry climate and orchard/trellis vegetable crops; and eastern Washington, with a hot/dry climate and orchard crops.

EPA has found the field and laboratory quality assurance/quality control (QA/QC) descriptions to be robust. The scenario is well defined. The protocol has addressed the technical aspects of applicable exposure monitoring guidelines, including the draft EPA Series 875 Group A: Applicator Monitoring Test Guidelines, Organization for Economic Cooperation and Development (OECD) Applicator Guidelines, and Good Laboratory Practices (40 CFR part 160). Acephate has been limited to an AaiH of 700 lbs, as is appropriate.

Clarifying Questions

Dr. Lebowitz asked if the behavior of the two surrogates was similar in terms of deposition, vapor pressure, particle or aerosol size, and absorption and inhalation properties to products used in typical agricultural work. Mr. Evans answered that exposure to the type of product being monitored (pesticides in WSPs) occurs primarily because of the dustiness of the product; other chemical aspects are not as important. Acephate is highly soluble, whereas carbaryl is less soluble. The two products have similar vapor pressures and have been

successfully used in other studies. Collection techniques, analyses, and QA/QC measures are very reliable for quantifying exposure to these products. Dr. Popendorf asked if the two products were equally dusty. Mr. Evans concurred they were if they leak out of the bags; the two products have similar particle size.

Dr. Popendorf questioned how EPA plans to use the data, for example, determining a mean or a percentile distribution. Mr. Evans explained that EPA will analyze all data gathered, determine the power of the proportionality assumption, and determine arithmetic means. The data also may be used to develop seasonal exposure assessments and explore frequency of use, range of active ingredient handled, and other factors that affect exposure. Dr. Lebowitz noted that if arithmetic means are calculated and a log normal distribution assumed, the 95-percent confidence interval based on geometric means intervals is not appropriate. Mr. Evans replied that the study design was meant to provide a three-fold range for arithmetic means and 95-percent confidence intervals. Analyses based on arithmetic mean and a log normal distribution are appropriate given EPA's intended use of the data; the data will not be used to describe a log normal distribution. Dr. Young expressed concern that the analyses had not been carefully planned.

Dr. Lebowitz asked if incorporating different areas and conditions into the sampling design would lead to different behaviors in the mixing process and thus different exposures. Mr. Evans confirmed that this was the case. Dr. Popendorf asked how handlers were recruited if the handlers themselves were commercial applicators; the design seems to imply that a commercial applicator working for a grower provides the MUs. Mr. Evans asked Dr. Popendorf to reserve this question for the AHETF representatives.

Dr. Popendorf noted that the revised protocol called for a group of experts to assess and characterize qualified handlers and asked if the qualified handlers would be reasonably representative of the grower populations as a whole. He asked how eligible growers might differ from typical growers. Ms. Sherman explained that this question would be addressed in EPA's ethics assessment.

EPA Ethics Assessment: AHE120

Ms. Sherman provided EPA's ethics assessment of the proposed scenario design and field study protocol. The protocol is expected to provide exposure data for workers who mix and load pesticides contained in WSPs; these data are needed to support EPA risk assessments. Studies conducted under this protocol will constitute the entire exposure data set for this scenario in the Agricultural Handler Exposure Database (AHED®). The knowledge gained from this work will be used to estimate dermal and inhalation exposure from the use of a wider range of agricultural pesticides available in WSPs. It is expected that these activities will result in better worker protection.

The proposed recruiting and consent processes support equitable subject selection, fully informed choice, fully voluntary choice, and respect for subjects. Exclusion and inclusion criteria are acceptable. Undue influence from employers is prevented. The processes allow for informed and voluntary choice and subjects are free to withdraw at any time.

The risks have been fully identified and effectively minimized; residual risks to subjects will be low. EPA judges the risks to subjects to be acceptable, given the potential societal benefits including improved risk assessment and protection of pesticide handlers.

IIRB has reviewed and approved the protocol and informed consent materials. IIRB is independent of the sponsors and investigators, registered with OHRP, and is seeking accreditation from AAHRPP. This IRB's "Human Research Protection Program Plan" was included with the LNX-002 materials. EPA has found no deficiencies relative to 40 CFR part 26, subparts K and L, or to FIFRA 12(a)(2)(P). All issues of concern previously identified by EPA and the HSRB have been satisfactorily addressed. Twenty-one of 24 issues in the Scenario Design and Field Study Protocol have been addressed; the 3 remaining issues were addressed in the AHETF's Response to EPA's Science and Ethics Review (dated May 12, 2009). EPA commends the AHETF for its responsiveness to concerns raised by the Agency and the HSRB.

Some concerns remain related to representativeness, presentation of individual exposure data, and localization of Spanish translations. There is some concern whether the study participants are representative of the target population of growers and commercial applicators. Past AHETF efforts to address this concern were unsuccessful. Thus, the AHETF has proposed to characterize eligible growers (e.g., by number of employee applicators, use of commercial applicators, use of pesticides or WSPs, type of crops, and season when pesticide is applied), both those who are willing and those unwilling to participate. Experts with local knowledge, including county extension personnel and local pesticide dealers, will be asked to assess characteristics of the willing and unwilling growers to determine representativeness. EPA believes that this will render the AHETF proposal effective and ethically acceptable. Regarding individual exposure data, there were concerns that workers who learn that their exposure is lower than average might become complacent or adopt riskier behavior. The AHETF has proposed to include with monitoring results a letter conveying the importance of diligence in the handling of pesticide, regardless of workers' individual exposure level; graphics depicting exposure distribution across body parts for the individual worker and the group average; and an EPA brochure describing safe practices for pesticide handlers. The Agency is satisfied with these changes. EPA also was concerned that the Spanish translations of study documents did not adequately reflect specific terminology and wording common to the study locale. The AHETF proposed to modify the documents as appropriate to meet local needs; contact people in different regions of the country who provide pesticide safety training to Spanish-speaking agricultural workers; ask reviewers to suggest changes in wording that would improve understanding in their geographic area; and ask reviewers to suggest translations for certain agricultural terms. EPA views these proposals favorably and these changes will ensure that the AHETF proposal is effective and ethically acceptable.

This is a proposal for third-party research involving intentional exposure of human subjects to a pesticide, with the intention of submitting the resulting data to EPA under the pesticide laws. The primary ethical standards applicable to the conduct of this research are 40 CFR part 26, subparts K and L. EPA has determined that the protocol meets the applicable requirements of these standards.

Clarifying Questions

Dr. Chambers asked if MSDS and safety procedure information would be distributed to all participants. Ms. Sherman answered that this information would be provided to all participants who request their exposure information.

Dr. Popendorf requested clarification of the decision to limit acephate to 700 lbs active ingredient. Mr. Evans answered that this decision was based on calculation of the combined MOE, which was based on toxicity endpoint data from a previous worker exposure study (21 day dermal and 21 day inhalation exposure study). The amount of acephate handled and rate at which it will be handled is compared to data from the toxicity study to determine an MOE that is the ratio between human exposure and the toxic endpoint. Dr. Popendorf asked how maximum AaiH (in lbs per day) was compared to dose. Mr. Carley explained that EPA starts from an MOE of 100, which is developed using estimated exposure and animal toxicity endpoints. Back calculations determined the 700-lb limit. Mr. Jordan added that EPA is calculating the exposure a mixer and loader would experience if working with 700 lbs of acephate during the course of the experiment. The study under discussion proposed to measure exposure, but Pesticide Handler Exposure Database data is used to predict exposure.

Dr. Philpott asked if the WSPs were designed to decrease the likelihood of handler exposure. Mr. Evans confirmed that this was the case. Dr. Philpott asked if there were any different routes of exposure or risk that use of WSPs would pose compared to those described in previous mixing and loading exposure studies. Mr. Evans answered that this was the first mixing and loading scenario reviewed by the Board. The WSPs are a risk-mitigation option with lower exposure potential.

Clarifying Questions for Principal Investigator/Sponsor

Dr. Richard Collier, AHETF and Dr. Victor Canez, AHETF

Dr. Philpott requested clarification regarding the identity and qualifications of the local experts who will help determine if those chosen to participate in the study are representative of growers and commercial applicators in the area. Dr. Canez answered that advice from extension agents will be sought; extension agents are familiar with the local handlers, growers, and agricultural conditions. As more information is obtained, a Master Grower List will be characterized; however, not all those contacted will provide information. As decisions are made regarding who will be asked to participate, more and more information will be available regarding types of crops, pesticides and equipment types used, and pesticide use patterns. Once this information is organized, extension agents will be asked to assess how well it represents local conditions.

Dr. Lebowitz noted that the protocol called for some minor scripting of behavior in an attempt to overcome possible small (undetectable) exposures. He asked how the AHETF would rectify situations in which actual exposures are different than predicted. Dr. Canez clarified that the scripting consisted of asking mixers/loaders to work for 4 hours per day and perform 3 mixing/loading applications. Dr. Lebowitz asked how the AHETF would handle exposures

that were too small to detect. Dr. Collier replied that to ensure exposure is not underestimated if different products with different active ingredients are used, the protocol calls for at least 3 mixing and loading operations. The AHETF expects to observe the lowest exposure in the lower AaiH strata. The resulting data could actually overestimate exposure from typical activities because of scripting; thus, any measurement error would result in a more protective exposure estimate. Dr. Popendorf inquired how the time would affect exposure calculations, given the need for 3 mixing and loading operations. Dr. Collier explained that the AHETF expects that EPA will calculate exposure based on AaiH and on an hourly basis and then extrapolate this to a typical work day. To minimize the degree of extrapolation, the protocol calls for participants to work at least 4 hours per day.

Dr. Chambers asked whether three applications would exceed the limits of the lower strata of active ingredient to be handled. Dr. Canez answered that the AHETF was currently unsure of the size of the packages and how this would impact the loading requirements.

Dr. Philpott requested clarification of the statement allowing study participants to refuse medical treatment unless experiencing medical problems directly related to pesticide exposure or heat, or if the participant could not make a rational decision. He noted that medical treatment cannot be forced on an unwilling person and it is difficult to determine if a person is capable of making a rational decision. Dr. Canez agreed that the AHETF would need guidance from medical personnel onsite regarding this issue. The goal of the AHETF is to provide the participant with whatever care is required at the time. Participants will not be forced to go to a hospital, but the AHETF will be diligent in addressing their medical needs. Dr. Collier noted that a symptom of heat stress is lack of cognitive power. If medical personnel believe a participant is experiencing heat stress, it might be safe to assume that the participant is temporarily incompetent. Regarding possible pesticide exposure, the AHETF wishes to be sure that rapid and appropriate treatment is obtained. Dr. Collier offered to change the language of this part of the documentation according to the Board's instructions.

In response to previous questions, Dr. Canez explained that commercial applicators will be involved in the protocols through the growers. Phone lists for recruitment are based on growers; if a grower wishes to participate, that grower will provide applicator contact information and the applicator fills the grower slot in the sampling procedure.

Dr. Collier and Dr. Canez did not offer to correct any matters in the EPA's assessment of the protocol.

Public Comments

Dr. Philpott invited oral public comment on the AHETF scenario design and field study protocol. No oral public comments were presented.

Board Discussion

Scientific Considerations – AHE120

Dr. Lebowitz opened the science discussion by noting that the description of sample size selection and other aspects of sample design and analysis are unclear; this poses serious problems for the reliability of the data. Given the amount of variability in MU selection, and the lack of scripting for the intended exposure, replication of the study using different MUs would likely lead to different exposure results. He added that the QA/QC plans and SOP revisions were appropriate.

Dr. Lebowitz stated that the sponsors have made major assumptions about the natural variation likely to occur, but most of it is ignored in the analysis plans; it is assumed that these variations represent diversity, but there is insufficient information to prove this. Accounting for natural variation in the statistical analyses will be difficult. The sponsors also claim that duration of monitoring is another parameter that could vary among MUs, especially because the AaiH would vary by more than two orders of magnitude. The AHETF contends that their approach will tend to overestimate exposure at the upper end of AaiH and underestimate exposure at the lower AaiH strata. They also claim that, given the small sample sizes, these estimations of bias are probably trivial relative to ordinary uncertainties due to sampling.

The sponsor's use of the term "random sampling" is inaccurate in some cases and thus problematic. Also, the statement that the monitoring data will be treated as if it were collected as a two-stage random sample from an infinite population is not accurate, because this is clearly a non-random, non-population based sample. Thus, their mixed model of approaches is not statistically valid.

Given the use of purposive sampling in an intentional exposure study, it is curious that the sponsors did not design a scripted study. In addition, for regulatory approaches, monitoring exposures occurring at the higher end of AaiH strata probably would be sufficient; these strata should be more heavily monitored. The Board has previously proposed changes to sampling design with respect to AaiH strata. In addition, other exposure studies that used population-based sampling found that oversampling at the 50^{th} percentile of AaiH and above would have been sufficient for regulatory purposes.

Dr. Lebowitz concluded that the data are likely to be scientifically adequate and sufficiently useful for assessing the exposures of these individuals, but that his conclusions were predicated on the dearth of prior scientifically reliable and sound data for this type of exposure research. The approach to purposive sampling could be more purposive and thus less expensive and more effective for reaching the aims and objectives put forth by the AHETF.

Dr. Popendorf agreed with Dr. Lebowitz's concerns regarding purposive sampling and AaiH stratification. Rather than recommend a different approach, Dr. Popendorf's main concern was that by stratifying the data as is currently described, statistically unusable data will be generated. It will be possible to determine mean and median, but if the distribution of AaiH in the real world is not similar to these strata, exposure will be particularly different at the higher

end of AaiH. Knowing the real-world distribution of AaiH would be helpful. This information could be gleaned from the local experts who will help develop and characterize lists of growers. He noted that the AHETF plans to characterize growers by 7 key points, but more information could help better understand real-world AaiH strata and thus make the results of the study more applicable. Dr. Popendorf expressed concern that once the data are in the database, users might forget that it was stratified when determining exposures; he suggested that the database contain information to alert users to this to avoid inappropriate mean calculation. The AHETF must recognize the limits of this stratified design.

Dr. Popendorf also commented on the artificial constraint of the protocol; requiring three tank loads to be mixed/loaded seems reasonable, but requiring a fourth seems artificial. Depending on whether EPA assesses exposure based on amount of pesticide used or duration of exposure will affect the validity of this approach. If exposure is based on AaiH, the amount of time spent mixing and loading will be less important and requiring a fourth tank load might not be necessary.

Dr. Popendorf commended the AHETF on the plans to inform participants about their exposure, but questioned the decision to provide this information once protocols were complete within a given cluster. This decision was based on the perceived need to deliver exposure results as soon as possible; however, each cluster will have only one MU from each strata of AaiH. It might be better to wait until all data are generated to permit comparisons of exposure within AaiH strata rather than cluster. Dr. Popendorf concluded his discussion by noting that protocol development and review had taken a long time, but that careful deliberations will likely save the AHETF money by ensuring that the protocol is sound and will deliver useable data.

Dr. Chambers clarified that 5 AaiH strata were planned based on the hypothesis that AaiH was proportional to exposure; the data could be used to generate an exposure model based on AaiH, but was not meant to generate a mean for all worker activity. Mr. Jordan agreed that if the assumption of proportionality is true, when the exposures and the AaiH are assessed for different strata, the calculations for each individual would be the same, although these are different individuals working with different equipment, and different amounts of active ingredient. If the proportionality assumption is not true, EPA will use the data to determine if or how predictive the amount of AaiH was. If there is no relationship, EPA will use the data to try to identify other predictors of exposure.

Dr. Johnson clarified that the Board had previously decided that it would judge whether the design type would provide useful information, not necessarily data that could be legitimately statistically analyzed. In the final report for the open- and closed-cab exposure studies, the Board recommended that EPA reconsider the design of the study or develop explicit statements regarding limits on the use of the data. He stated that the Board should not recommend redesign of the study, but should caution EPA and the AHETF to be careful regarding statistical analyses. As it stands, the protocol will generate data that can be used to determine mean and standard deviation, but limits should be placed on how the data can be used.

Dr. Philpott agreed that the comments made by the reviewers were valid; however, given that the Board had favorably reviewed similar protocols in the past, any substantive changes

recommended for this protocol might require the Board to review and modify its previous recommendations. The Board has discussed limitations of these studies in the past and has recommended that EPA be cognizant of these limits; however, the Board should be cautious about recommending changes to the protocol that deviate from precedent unless there is a serious need for these changes. Dr. Lebowitz agreed and noted that his comments constituted a critique rather than recommendations. Using a multi-stage or two-stage AaiH stratification scheme will not significantly affect the data, and he recognized that the AHETF was unlikely to redesign the protocol to incorporate total scripting of worker activities.

Dr. Philpott asked if the Board believed that, given the limitations of sampling and the types of statistical analyses that can be performed on these data, the protocol will generate scientifically reliable data that EPA can use to assess exposure occurring during mixing and loading of WSPs. He noted Dr. Johnson's suggestion that the Board explicitly state the limits on the use of the data. Dr. Philpott also suggested that the sponsors and EPA consider the limits of the statistical analyses that can be performed on these data and in the future de-emphasize these analyses in their protocols. Given these two conditions, the Board believes the data generated will be scientifically reliable.

Ethical Considerations – AHE120

Dr. Philpott agreed with EPA's review and assessment of the protocol, with a few minor exceptions. The protocol is well designed to minimize risk, is respectful of subjects, and appropriately seeks and ensures voluntary and informed participation. Thus, the protocol meets the requirements of 40 CFR part 26. Because of the use of whole-body dosimeters, the subjects are at greater than minimal risk for heat-related illnesses. He commended the AHETF's close attention to both heat and humidity and in developing stopping rules to minimize the danger of heat-related illnesses. He expressed concern that the guidelines concerning heat-related illness are based on a 150-lb. male wearing a light-weight shirt, long pants, and walking at a moderate speed in the shade. Dr. Philpott agreed that mixing and loading are generally light-duty tasks, but because participants are required to wear a whole-body dosimeter in addition to their usual clothes, the AHETF might want to be more conservative about the temperature at which work will be stopped (currently 120^{o} F). Ms. Sherman clarified that the AHETF recently revised the stopping point to a 105^{o} F heat index. Dr. Philpott agreed that this was appropriate and adequately addressed his concern. He added that another minor concern was that some of the investigators involved in this study will need to update their human subject research training and certification soon.

Dr. Philpott noted three issues raised by the AHETF as needing further input and advice from the Board. The first issue relates to the challenges faced by the AHETF for ensuring representativeness of growers. Dr. Philpott stated that their current approach is reasonable, with the caveat that it might be possible to obtain further information about growers and better inform sample design; however, the AHETF faces challenges for obtaining complete information about all growers in an area because some may refuse to respond to questions. Given these difficulties, the AHETF's plan for ensuring representativeness is adequate.

Secondly, Dr. Philpott agreed with Dr. Popendorf's conclusion that release of individual exposure data could be delayed to give the participants an accurate assessment of their exposure with respect to AaiH. Providing these data constitutes respect to subjects and a commendable addition to the protocol. Dr. Philpott added that if a particular participant shows evidence of an unusually high level of exposure, it would be permissible to contact this participant sooner to help mitigate risk.

The third issue relates to the Spanish translation of the protocol documents and ICF. Dr. Philpott commended the AHETF's efforts to ensure an appropriate and accurate translation of these documents. He recognized the difficulties associated with this task, given the different Spanish dialects spoken across the United States.

Dr. Philpott's final recommendation was to advise the AHETF to seek involvement of farm worker representatives or other members of the community, particularly for recruitment activities and meetings for participants. Members of the community can be helpful for recruitment and retention and for identifying unanticipated challenges to working with this population. He concluded that all ethical requirements for this protocol had been met. Prof. Meisel agreed with Dr. Philpott's assessment and had no further comments.

Summary of Board Response to the Charge Questions

Is the research likely to generate scientifically reliable data, useful for assessing the exposure of handlers who mix and load soluble or wettable powder pesticides in water-soluble packaging?

The Board concluded that the proposed research is likely to generate some scientifically reliable data, but recommended that EPA acknowledge the limitations of these data under the proposed study design, perhaps by developing an explicit statement on the utility of the data relative to the proposed study design and statistical limitations. The Board also recommended that the Agency and Task Force de-emphasize the statistical analyses of the data in future protocols and reports.

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

The Board concluded that the research is likely to meet the applicable requirements of 40 CFR part 26, subparts K and L. The Board also recommended that the Task Force implement the proposed protocol changes designed to address issues of representativeness and language. With respect to presentation of individual exposure data, the Board recommended delaying release of individual data until all analyses of representative MUs were complete, except in instances where the data suggest unusually high exposure.

Concluding Remarks

Mr. Jordan complimented the Board on their efforts at this meeting and the clarity of their advice and recommendations. He thanked Board members and consultants for their efforts in preparing for the meeting.

Dr. Philpott acknowledged the efforts of the Board, particularly given the reduced number of Board members and the number of documents members were required to review. He thanked the consultants and recognized the challenges posed to them at this meeting, given their lack of previous knowledge regarding Board activities and the large amount of information discussed.

Dr. Lewis thanked Dr. Philpott for serving as Chair and Dr. Parkin for serving as Vice Chair. He thanked the Board members and consultants for their preparation for and efforts at this meeting.

The Board will prepare a report responding to the charge questions posed by EPA. Members may work with consultants when crafting their responses; Dr. Lewis reiterated that consultants may provide advice, but do not participate in the Board deliberation processes. A draft of the Board report will be posted on the HSRB Web site and www.regulations.gov as soon as possible. The report will be reviewed and finalized during a teleconference or at the next face-to-face meeting; an announcement of this review will be made in the *Federal Register*. The next HSRB meeting will be October 20-23, 2009 at the EPA facility in Crystal City, VA. Specific times and dates will be announced in the *Federal Register*.

The meeting was adjourned by the Chair and DFO.

Respectfully submitted:

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

Certified to be true by:

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

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

Attachments

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

Attachment A

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* Not in attendance at the June 24-25, 2009 Meeting

Attachment B

Federal Register Notice Announcing Meeting

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

[Federal Register: June 4, 2009 (Volume 74, Number 106)]
[Notices]
[Page 26861-26863]
From the Federal Register Online via GPO Access [wais.access.gpo.gov]

ENVIRONMENTAL PROTECTION AGENCY
[EPA–HQ–ORD–2009–0183; FRL–8913–9]

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

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

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

DATES: The public meeting will be held from June 24, 2009 from approximately 9:30 a.m. to approximately 5:30 p.m., through June 25, 2009 from approximately 8:30 a.m. to approximately 4:30 p.m. (Eastern Time).

Location: Holiday Inn National Airport, 2605 Jefferson Davis Highway (Crystal City), Arlington, VA 22202 (703) 684–7200).

Meeting Access: Seating at the meeting will be on a first-come basis. To request accommodation of a disability please contact the person listed under **FOR FURTHER INFORMATION CONTACT** at least 10 business days prior to the meeting, to allow EPA as much time as possible to process your request.

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

FOR FURTHER INFORMATION CONTACT: Any member of the public who wishes further information should contact Jim Downing, EPA, Office of the Science Advisor, (8105R), Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460; telephone number: (202) 564–2468; fax: (202) 564–2070; e-mail addresses: *downing.jim@epa.gov.* General information concerning the EPA HSRB can be found on the EPA Web site at *http://www.epa.gov/osa/hsrb/.*

ADDRESSES: Submit your written comments, identified by Docket ID No. EPA–HQ–ORD–2009–0183, 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 email the ORD Docket at *ord.docket@epa.gov* for instructions. Updates to Public Reading Room access are available on the Web site (*http:// www.epa.gov/epahome/dockets.htm*).

Instructions: Direct your comments to Docket ID No. EPA–HQ–ORD–2009– 0183. EPA's policy is that all comments received will be included in the public docket without change and may be made available online at *http:// www.regulations.gov,* including any personal information provided, unless the comment includes information claimed to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Do not submit information that you consider to be CBI or otherwise protected through *http:// www.regulations.gov* or e-mail. The *http://www.regulations.gov* website is an ''anonymous access'' system, which means EPA will not know your identity or contact information unless you provide it in the body of your comment. If you send an e-mail comment directly to EPA, without going through *http:// www.regulations.gov,* your e-mail address will be automatically captured and included as part of the comment that is placed in the public docket and made available on the Internet. If you submit an electronic comment, EPA recommends that you include your name and other contact information in the body of your comment and with any disk or CD–ROM you submit. If EPA cannot read your comment due to technical difficulties and cannot contact you for clarification, EPA may not be able to consider your comment. Electronic files should avoid the use of special characters, any form of encryption, and be free of any defects or viruses.

SUPPLEMENTARY INFORMATION:

I. Public Meeting

A. Does This Action Apply to Me?

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

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

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

Docket: All documents in the docket are listed in the *http:// www.regulations.gov* index. Although listed in the index, some information is not publicly available, *e.g.,* CBI or other information whose disclosure is restricted by statute. Certain other material, such as copyrighted material, will be publicly available only in hard copy. Publicly available docket materials are available either electronically in *http:// www.regulations.gov* or in hard copy at the ORD Docket, EPA/DC, Public Reading Room. The EPA/DC Public Reading Room is located in the EPA Headquarters Library, Room Number 3334 in the EPA West Building, located at 1301 Constitution Ave., NW., Washington, DC. 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 email the ORD Docket at *ord.docket@epa.gov* for instructions. Updates to Public Reading Room access are available on the Web site (*http:// www.epa.gov/epahome/dockets.htm*).

EPA's position paper(s), charge/ questions to the HSRB, and the meeting agenda will be available by early June 2009. In addition, the Agency may provide additional background documents as the materials become available. You may obtain electronic copies of these documents, and certain other related documents that might be available electronically, from the regulations.gov website and the EPA HSRB website at *http://www.epa.gov/ osa/hsrb/.* For questions on document availability or if you do not have access to the Internet, consult the person listed under **FOR FURTHER INFORMATION**.

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

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

a. Explain your views as clearly as possible.
b. Describe any assumptions that you used.
c. Provide copies of any technical information and/or data 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–2009– 0183 in the subject line on the first page of your request.

a. *Oral comment*

Requests to present oral comments will be accepted up to June 17, 2009. To the extent that time permits, interested persons who have not pre-registered may be permitted by the Chair of the HSRB to present oral comments at the meeting. Each individual or group wishing to make brief oral comments to the HSRB is strongly advised to submit their request (preferably via e-mail) to the person listed under **FOR FURTHER INFORMATION CONTACT** no later than noon, Eastern time, June 17, 2009 in order to be included on the meeting agenda and to provide sufficient time for the HSRB Chair and HSRB Designated Federal Officer (DFO) to review the agenda to provide an appropriate public comment period. The request should identify the name of the individual making the presentation, the organization (if any) the individual will represent, and any requirements for audiovisual equipment (*e.g.,* overhead projector, LCD projector, chalkboard). Oral comments before the HSRB are limited to five minutes per individual or organization. Please note that this limit applies to the cumulative time used by all individuals appearing either as part of, or on behalf of an organization. While it is our intent to hear a full range of oral comments on the science and ethics issues under discussion, it is not our intent to permit organizations to expand these time limitations by having numerous individuals sign up separately to speak on their behalf. If additional time is available, there may be flexibility in time for public comments. Each speaker should bring 25 copies of his or her comments and presentation slides for distribution to the HSRB at the meeting.

b. *Written comment*

Although you may submit written comments at any time, for the HSRB to have the best opportunity to review and consider your comments as it deliberates on its report, you should submit your comments at least five business days prior to the beginning of the meeting. If you submit comments after this date, those comments will be provided to the Board members, but you should recognize that the Board members may not have adequate time to consider those comments prior to making a decision. Thus, if you plan to submit written comments, the Agency strongly encourages you to submit such comments no later than noon, Eastern Time, June 17, 2009. You should submit your comments using the instructions in

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

E. Background

A. Topics for Discussion

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

The June 24–25, 2009 meeting of the Human Studies Review Board will address scientific and ethical issues surrounding:

Four unpublished reports of research completed before enactment of the 2006 expanded EPA Regulation 40 CFR part 26 (Protection of Human Subjects rule) on the organophosphate pesticide chlorpyrifos:

- A study by Coulston *et al.* (1972) of the subacute oral toxicity of chlorpyrifos to adult male prisoners.
- A study by Nolan *et al.* (1982) of the metabolism and excretion of chlorpyrifos and cholinesterase activity in adult males after a single oral or dermal exposure.
- A study by Honeycutt and DeGeare (1993) monitoring the Acetylcholinesterase activity and urinary metabolites of chlorpyrifos in agricultural workers who re-entered chlorpyrifos-treated citrus groves.
- A study by Kisicki *et al.* (1999) of the acute oral toxicity of chlorpyrifos to adult male and female volunteers.
- A proposal for new research to be conducted by Carroll-Loye Biological Research to evaluate the repellent efficacy to biting flies in the field of two registered products containing 20% picaridin.
- The report of a completed laboratory study conducted by ICR, Inc., to evaluate the repellent efficacy to stable flies of two registered products containing 20% picaridin.
- A new scenario design and associated protocol for field studies at five sites from the Agricultural Handlers Exposure Task Force (AHETF), describing proposed research to monitor exposure of professional pesticide handlers who mix and load pesticides formulated as wettable powders in water-soluble packaging.

In addition, the Board will be reviewing its draft February 17, 2009 meeting report for subsequent Board approval. Finally, the HSRB may also discuss planning for future HSRB meetings.

B. Meeting Minutes and Reports

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

Dated: May 29, 2009.
Kevin Teichman,
EPA Acting Science Advisor.
[FR Doc. E9–13061 Filed 6–3–09; 8:45 am]
BILLING CODE 6560–50–P

Attachment C

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
HUMAN STUDIES REVIEW BOARD (HSRB)
JUNE 24-25, 2009
PUBLIC MEETING

JUNE 24, 2009
Holiday Inn National Airport
2650 Jefferson Davis Highway
Arlington, VA
(703) 684 7200

HSRB WEB SITE http://www.epa.gov/osa/hsrb/
Docket Telephone: (202) 566 1752
Docket Number: EPA-HQ-ORD-2009-0183

- **9:30 AM** **Convene Meeting and Administrative Procedures –** Paul Lewis, Ph.D. (Designated Federal Officer, EPA Human Studies Review Board, Office of the Science Advisor, EPA)
- **9:40 AM** **Introduction and Identification of Board Members** – Sean Philpott, Ph.D. (HSRB Chair)
- **9:50 AM** **Welcome –** Kevin Teichman, Ph.D. (Acting Science Advisor, Office of the Science Advisor, EPA)
- **10:00 AM** **Opening Remarks –** Debbie Edwards, Ph.D. (Director, Office of Pesticide Programs [OPP], EPA)
- **10:10 AM** **EPA Follow-up on Pesticide Specific HSRB Recommendations –** Mr. William Jordan (OPP, EPA)

Chlorpyrifos Human Toxicity Studies

- **10:15 AM** **EPA Science and Ethics Reviews –** Anna Lowit, Ph.D. (OPP, EPA), John Doherty, Ph.D. (OPP, EPA), Mr. Wade Britton (OPP, EPA), and Mr. John Carley (OPP, EPA)

  Board Questions of Clarification – Sean Philpott, Ph.D. (HSRB Chair)
  EPA -
  Principal investigator/sponsor -
- **12:00 PM** **Lunch**
- **1:00 PM** **Public Comments**
- **1:15 PM** **Review and Discussion of HSRB Approaches for Consideration of Pre-Rule Human Dosing Studies –** Sean Philpott, Ph.D. (HSRB Chair)
- **2:15 PM** **Board Discussion**

The Agency is taking a new path in its assessment of chlorpyrifos, basing the RfD on data from pregnant rats, fetuses, and post-natal rats. Since the available human studies address only cholinesterase inhibition rather than other endpoints, they are not directly relevant to the forthcoming risk assessment focused on pregnant women and children. EPA proposes to use the three human studies listed below to characterize and help interpret epidemiological and biomonitoring data, using bounding estimates as described in the White Paper and potentially using physiologically-based pharmacokinetic (PBPK) models.

1.1 Nolan *et al.* (1982)

1.1.1 Are the blood and urine measurements of chlorpyrifos and/or TCP from the Nolan *et al.* oral and dermal studies reliable?

1.1.2 Are the measurements of cholinesterase activity/inhibition from the Nolan *et al.* oral and dermal studies reliable?

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

1.2 Honeycutt and DeGeare (1993)

1.2.1 Are the blood and urine measurements of chlorpyrifos and/or TCP from the Honeycutt and DeGeare worker biomonitoring study reliable?

1.2.2 Are the measurements of cholinesterase activity/inhibition from the Honeycutt and DeGeare worker biomonitoring study reliable?

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

1.3 Kisicki *et al.* (1999)

1.3.1 Are the blood and urine measurements of chlorpyrifos and/or TCP from the Kisicki *et al.* oral study reliable?

1.3.2 Are the measurements of cholinesterase activity/inhibition from the Kisicki *et al.* oral study reliable?

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

- **4:00 PM Break**
- **4:15 PM Board Summary**

Review of February 17, 2009 HSRB Meeting Report

- **4:45 PM** **Review Process –** Sean Philpott, Ph.D. (HSRB Chair)
- **4:50 PM** **Public Comments**
- **5:00 PM** **Board Discussion and Decision on Report –** Sean Philpott, Ph.D. (HSRB Chair)
- **5:45 PM** **Concluding Remarks –** Mr. William Jordan (OPP, EPA)
- **5:50 PM** **Adjournment** – Sean Philpott, Ph.D. (HSRB Chair) and Paul Lewis, Ph.D. (HSRB DFO)

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
HUMAN STUDIES REVIEW BOARD (HSRB)
JUNE 24-25, 2009 *
PUBLIC MEETING

JUNE 25, 2009

Holiday Inn National Airport
2650 Jefferson Davis Highway
Arlington, VA
(703) 684 7200

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

Carroll-Loye Biological Research, Inc. Protocol LNX-002: Efficacy of Picaridin-Based Personal Insect Repellents against Biting Flies in the Field

- **8:45 AM** **EPA Science and Ethics Reviews –** Mr. Kevin Sweeney (OPP, EPA) and Mr. John Carley (OPP, EPA)
- **9:30 AM** **Board Questions of Clarification** – Sean Philpott, Ph.D. (HSRB Chair)
  EPA -
  Principal investigator/sponsor -
- **9:50 AM** **Public Comments**
- **10:05 AM** **Board Discussion**

If the proposed field repellency study protocol LNX-002 is revised as suggested in EPA's review and if the research is performed as described:

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

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

- **10:55 AM** **Break**
- **11:10 AM** **Board Summary**

ICR, Inc. Study A382: Efficacy of Picaridin-Based Personal Insect Repellents against Stable Flies in the Laboratory

- **11:25 AM** **EPA Science and Ethics Reviews –** Mr. Kevin Sweeney (OPP, EPA) and Mr. John Carley (OPP, EPA)
- **12:00 PM** **Board Questions of Clarification** – Sean Philpott, Ph.D. (HSRB Chair)
  EPA -
  Principal investigator/sponsor –

- **12:15 PM Lunch**
- **1:00 PM Public Comments**
- **1:15 PM Board Discussion**

1. Is the ICR study A382 sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy of the tested formulations against stable flies in the laboratory?

2. Does available information support a determination that study A382 was conducted in substantial compliance with subparts K and L 40 CFR Part 26?

- **2:00 PM Break**
- **2:15 PM Board Summary**

Agricultural Handlers Exposure Task Force (AHETF) Scenario Design and Field Study Protocol: Mixing /Loading Wettable Powder in Water Soluble Packaging

- **2:30 PM EPA Science and Ethics Reviews –** Mr. Jeff Evans (OPP, EPA) and Ms. Kelly Sherman (OPP, EPA)
- **3:30 PM Board Questions of Clarification** – Sean Philpott, Ph.D. (HSRB Chair)
  EPA -
  Principal investigator/sponsor –
- **3:50 PM Public Comments**
- **4:05 PM Board Discussion**

If the proposed mix/load water soluble packing field study protocol AHE120 is revised as suggested in EPA's review and if the research is performed as described:

1. Is the research likely to generate scientifically reliable data, useful for assessing the exposure of handlers who mix and load soluble or wettable powder pesticides in water-soluble packaging?

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

- **5:05 PM Board Summary**
- **5:20 PM Concluding Remarks –** Mr. William Jordan (OPP, EPA)
- **5:25 PM Adjournment** – Sean Philpott, Ph.D. (HSRB Chair) and Paul Lewis, Ph.D. (HSRB DFO)

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