May 7, 2007

Minutes of the
United States Environmental Protection Agency (EPA)
Human Studies Review Board (HSRB)
April 18-20, 2007 Public Meeting
Docket Number: EPA-HQ-ORD-2007-0216
HSRB Web Site: http://www.epa.gov/osa/hsrb/

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

Dates and Times:	Wednesday, April 18, 2007, 10:00 AM – 5:30 PM Thursday, April 19, 2007, 8:30 AM – 5:30 PM Friday, April 20, 2007, 8:30 AM – 5:30 PM (See Federal Register Notice – Attachment B)	
Location:	Environmental Protection Agency, One Potomac Yard (South Bldg.), 2777 S. Crystal Drive, Arlington, VA 22202	
Purpose:	The EPA Human Studies Review Board (HSRB) provides advice, information, and recommendations on issues related to the scientific and ethical aspects of human subjects research.	
Attendees:	Chair:	Celia B. Fisher, Ph.D.
	Vice Chair:	William S. Brimijoin, Ph.D.
	Board Members:	Alicia Carriquiry, Ph.D. Gary L. Chadwick, PharmD, MPH, CIP Janice Chambers, Ph.D., D.A.B.T. Richard Fenske, Ph.D., MPH Susan S. Fish, PharmD, MPH Suzanne C. Fitzpatrick, Ph.D., D.A.B.T. KyungMann Kim, Ph.D., CCRP Kannan Krishnan, Ph.D. Michael D. Lebowitz, Ph.D., FCCP Lois D. Lehman-Mckeeman, Ph.D. Jerry A. Menikoff, M.D. Sean M. Philpott, Ph.D. Richard Sharp, Ph.D.
Meeting Summary:	Meeting discussions generally followed the issues and general timing as presented in the meeting Agenda (Attachment C), unless noted otherwise in these minutes.	

Introduction and Identification of Board Members

Dr. Celia Fisher (HSRB Chair) welcomed Board members, U.S. Environmental Protection Agency (EPA or Agency) staff, and members of the public to the April 2007 HSRB meeting. She thanked Board members for their participation and called for introductions. Dr. Fisher acknowledged the efforts of Dr. Paul Lewis (Designated Federal Officer [DFO], HSRB, Office of the Science Advisor [OSA], EPA) and members of EPA's Office of Pesticide Programs (OPP) in planning and preparing for this meeting.

Welcoming Remarks

Dr. Warren Lux (Human Subjects Research Review Official, OSA, EPA) welcomed and thanked the Board on behalf of Dr. George Gray (Science Advisor, EPA) and Dr. William H. Benson (Acting Chief Scientist, OSA. EPA). He commented that the last HSRB meeting represented the culmination of a complete review cycle from submission of a protocol to completion and use of the data in policies established by EPA.

Another Board activity of importance is education. Regulatory matters and protocol reviews are necessary to protect human subjects; however, educational efforts also are needed to ensure appropriate protection. Dr. Lux expressed appreciation for the Board's efforts and requests for education about matters pertinent to EPA and commended the Board's work to ensure its deliberations educate others, including OPP personnel, third party sponsors, investigators, and interested members of the public. He especially wished to highlight the impact of the Board's efforts on investigators, because fully educated, informed investigators will assure appropriate human subject protection.

Dr. Fisher thanked Dr. Lux for his comments and added that the Board will continue to learn from Dr. Lux. The Board expects input from EPA staff to contribute to the consistency of its review of sponsors and EPA in-house reviews, and may suggest ways to facilitate this exchange of information in the future.

Mr. Jim Jones (Principal Deputy Assistant Administrator, Office of Prevention, Pesticides, and Toxic Substances, EPA) welcomed Board members to Washington, DC. He stated that OPP continues to find Board advice helpful to gain EPA acceptance of study results and improve the quality of its feedback to investigators. The Agency implemented new rules for human subject studies in February 2006. At that time, there were controversies and doubts about whether the new rules would still permit EPA to meet its deadlines and work within the statutory framework. The HSRB developed a framework for review, provided EPA with sound advice, helped to settle controversies, and helped EPA adapt to these changes. Stakeholders are adjusting to the new rules and OPP is meeting critical statutory deadlines. Together, EPA and the HSRB have made significant progress in ensuring that human subjects are protected. He introduced Dr. Debbie Edwards as the new Director of OPP.

Dr. Edwards described her previous work as Director of the Special Review and Re-registration Division within OPP. She commented that the Board's high-quality reviews have allowed OPP to be successful. She provided a brief overview of the meeting agenda, explaining

that the focus of the first day of the meeting would be devoted to a review of recently conducted tick and mosquito repellency studies to support regulatory decisions. On April 19, 2007, the Board will discuss two previously performed skin test studies that will raise new scientific and ethical questions, as well as EPA's framework for developing best practices for subject recruitment for occupational exposure research. On April 20, 2007, the Board will discuss follow-up on the Agricultural Handlers Exposure Task Force (AHETF) and Antimicrobial Exposure Assessment Task Force (AEATF) protocols and will review a summary of the EPA Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) January 2007 report "Worker Exposure Methods." OPP also will present a draft framework for recruiting subjects and ethical considerations for occupational exposure studies.

Meeting Administrative Procedures

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

Dr. Fisher thanked OPP members for their remarks and commended their responsiveness to questions and requests from the Board for documents and information. She added that she was pleased to see the Board's recommendations incorporated into OPP analyses.

Dr. Fisher reviewed the meeting agenda. For the last few meetings, the Board has asked OPP to provide critiques of studies rather than summaries. Concerning discussion of the FIFRA SAP report, scheduled for April 20, 2007, the Board requested this discussion because of questions that arose during review of the handler protocol concerning why these studies were necessary.

Meeting Process

Dr. Fisher reviewed the process for meeting operations, HSRB responsibilities, the HSRB Charter, Board process, and major objectives. She stated that the Board seeks to clarify and develop criteria to evaluate the science and ethics of different types of completed research and protocols, allowing for fairness and consistency. A useful set of criteria for assessing scientific validity has been developed for sponsors and investigators providing protocols for review. These provide guidance for study design and materials needed for Board review of protocols. The Board assesses both the scientific and ethical validity of a protocol, including procedures, dose selection, endpoint selection, social value of the research, methods including statistical analyses, selection of target populations, and derivation of sample sizes. In its ethics assessments, the

Board considers both societal benefit and participant risks. It has worked to define prevalent ethical standards and to develop additional ethics criteria.

EPA Follow-up on HSRB Recommendations

Mr. William Jordan (OPP, EPA) reviewed EPA follow-up on HSRB recommendations for the completed IR3535 insect repellent efficacy studies with lotion and pump spray formulations, EMD-003.1 and 003.2 (laboratory tick repellency) and EMD-004.1 and 004.2 (field mosquito repellency). EPA follow-up on the field mosquito repellent efficacy protocol SCI-001 was also discussed.

Concerning the HSRB's scientific recommendations for the completed studies EMD-003.1 and 003.2 and EMD-004.1 and 004.2, the HSRB concluded that the studies were scientifically sound and suggested alternative statistical techniques for evaluating duration of efficacy. The Board also suggested that EPA consider the most appropriate way to conduct dosimetry studies to determine typical consumer dose. Based on these recommendations, EPA will accept the IR3535 insect repellent efficacy studies as adequate for the assessment of efficacy and will accept label claims.

EPA continues to discuss the best statistical approaches for analyzing data and determining duration of protection. A challenge to this effort is the existence of similar products on the consumer market that have Complete Protection Times (CPTs) that were determined differently in past studies. EPA is considering the best ways to implement the Board's suggestions and manage the transition to new methods of determining CPT. Once EPA has developed an approach to implement new statistical analysis methods, it will present the plan to the HSRB for feedback. EPA also plans to revise its draft repellent efficacy guidelines to include discussion of methods for establishing doses, based on typical consumer use.

Concerning ethics recommendations, HSRB concurred with EPA that these studies met the applicable requirements of 40 Code of Federal Regulation (CFR) 26, subparts K and L. The Board noted some ethical deficiencies and suggested that EPA recommend human research protection training for investigators. Based on this review, EPA will accept the IR3535 repellency studies. Although EPA cannot require investigators to complete human research protection training, it will informally encourage such training.

HSRB also reviewed SCI-001 at the January 24, 2007, meeting and found that the recommendations suggested by EPA and the Board were followed, and that this protocol was likely to generate scientifically valid data to assess the efficacy of the test products and to meet applicable ethics requirements. EPA agreed with the Board's assessment, but has not yet received a revised version of SCI-001 or the results of a completed study conducted under this protocol.

Completed Repellent Efficacy Studies EMD-003.3 and EMD-004.3

Introduction

Mr. John Carley (OPP, EPA) provided background and context for insect repellent efficacy studies EMD-003.3 and EMD-004.3. These studies tested the aerosol formulations of the IR3535 repellents tested as pump spray and lotion. Testing on the aerosol formulation was delayed because of a manufacturing error. EMD-003.3 tests repellency against ticks in a laboratory setting. EMD-004.3 tests repellency against mosquitoes in two field settings. Dosimetry testing for these formulations was performed on October 25-26, 2006, in conjunction with dosimetry testing for the other formulations. The report relating the results of EMD-003.4 and EMD-004.3 was submitted in December 2006, but was not provided to the HSRB for discussion at the January 2007 meeting. These studies, which represent third-party research involving intentional exposure of human subjects, were initiated after April 7, 2006, and were intended for submission to EPA under the pesticide laws. Pre-review of the protocols and supporting materials by EPA and the HSRB is required, as well as "substantial compliance" with 40 CFR 26 subparts K and L.

The execution and results of these protocols for the lotion and pump spray formulations were the first completed studies reporting work under post-rule protocols to be reviewed by the HSRB, and were reviewed favorably at the January 24, 2007 meeting. The HSRB review of both protocols EMD-003.3 and 004.3 took place on October 19, 2006. Subject limb measurement and dosimetry testing of all three formulations occurred between October 23 and November 1, 2006. Revisions to the protocols and informed consent forms (ICFs) were submitted to the Independent Investigational Review Board (IIRB) on October 30, 2006, and IIRB approval of final changes was granted on November 1, 2006. Field testing for protocol EMD-004.3 in Merced County, California, (marsh/grassland) took place on November 15, 2006, and field testing in Butte County, California, (forest/flooded marsh) occurred on November 19, 2006. Laboratory testing for EMD-003.3 took place on November 18, 2006. A final audit by the quality assurance (QA) unit was performed on November 10, 2006, and final study reports for both protocols were submitted on February 5, 2007. The dosimetry phase of these studies used the ICF changed by Dr. Scott Carroll (Carroll-Loye Biological Research, Inc.); the efficacy phase used the final November 1, 2006 ICF.

The dosimetry phase involved 12 subjects. Each subject's limb surface areas were calculated, subjects practiced application for "full coverage," four gauze "bracelet" dosimeters were placed on the limbs, and the weight change in dosimeters after application was measured. The subject mean of three trials was determined and then the grand mean of all 12 subject means was calculated. Based on limb surface area, the standard dose (gram per square centimeter [g/cm2]) was converted to a volumetric standard dose (milliliter per square centimeter [ml/cm2]) and scaled for each subject in the efficacy phase.

EMD-003.3, which tested tick repellency, involved 10 subjects in a laboratory setting. After application of a standard volumetric dose by syringe to the arm, both arms were marked at the edge of the untreated area and at the 3 centimeter (cm) mark on each side of the area. New ticks were placed near the wrist of the untreated arm and observed for questing behavior.

Questing ticks then were placed at the lowest mark of the treated arm and ticks crossing 3 cm or more into the treated area were scored as "crossing." A fresh tick was applied every 15 minutes. Time of efficacy failure was defined as the time of the first of two crossings occurring within 30 minutes.

EMD-004.3, which tested mosquito repellency, involved 10 treated subjects at each of two field sites. Two untreated subjects were present at each site to confirm mosquito biting pressure at the site. A standard volumetric dose scaled to the area of the subjects' lower legs was applied by syringe before traveling to the test site. The subjects wore Tyvek suits, head nets, and gloves and worked in pairs to expose treated legs by rolling up their pants for 1 minute every 15 minutes. The subjects watched for landings with intent to bite (LIBes), and removed these mosquitoes with aspirators. Landing mosquitoes were reported to technicians and recorded. Treated limbs were re-covered with the Tyvek suit at the end of each 1-minute exposure period. Time of efficacy failure (time to first confirmed LIBe [FCLIBe]) was defined as time post-treatment of the first of two LIBes occurring within 30 minutes.

Scientific Considerations

Dr. Clara Fuentes (OPP, EPA) presented the science assessments for EMD-003.3 and EMD-004.3. These studies were executed in a manner consistent with the revised protocols, with minor exceptions. The study designs produced scientifically sound data meeting the studies' objectives to estimate typical consumer doses and quantify the duration of repellency of the formulations tested against ticks and mosquitoes.

Deviations from the dosimetry phase of the protocol included a reduction in the number of pre-test practice applications from three to one; there were no data to suggest how this might have affected the dosimetry phase. Entry errors were not properly handled in all cases, but there was no obvious ambiguity in the records and the data quality does not appear to have been compromised. The dosimetry data capture forms were modified from those appended to the protocol, but the modification did not compromise data quality. The dosimeters were not backed with impermeable layers but appeared to be sufficiently impermeable to the test material without backing. The aerosol spray dosimeter results were not compared to those for the lotion and pump formulations, but these comparisons were not required to determine typical consumer dose for efficacy testing.

Half the subjects in EMD-003.3 withdrew from the study before a confirmed crossing into the treated area (i.e., before failure of efficacy) occurred. The original analysis of pre-failure withdrawals underestimated product performance. Because of this, the data were re-analyzed using the Kaplan-Meier method as suggested by the Board at its January 2007 HSRB meeting.

For EMD-004.3, test material was applied 2 to 3 hours before beginning field testing rather than at the site. Because the materials were effective for more than 8 hours, this was unlikely to have affected CPT results, because CPT was estimated from the time of repellent application to FCLIBe. The subjects did not always cover treated limbs between exposures, but stepped out of the test site or entered a screened enclosure. This was unlikely to have affected

the results because the treated limbs were not exposed to mosquitoes between scheduled exposure periods.

Calculated doses from the dosimetry phase were 0.00134 g/cm2 for arms and 0.000987 g/cm2 for legs. For the efficacy phase, the calculated dose for arms was 0.00143 ml/cm2, and for legs, 0.00105 ml/cm2; these did not vary significantly from the calculated target doses.

The efficacy phase for EMD-003.3 found a mean CPT of 10.95 hours, $\pm$2.8 hours with a 95% confidence interval of 9 to 13 hours. Range of subject CPT was 4.25 to 13.5 hours. After reanalysis using the Kaplan Meier method, the median CPT was determined to be 13 hours and time to 25 percent failures was 10.75 hours.

The efficacy phase for EMD-004.3 found a CPT of 9.65 hours, ±0.32 hours, with a range of 8.75 to 9.75 hours and 95% confidence interval of 9.45 to 9.88 hours for testing at the forest site. At the marsh/pasture site, no confirmed landings occurred and all exposures were ended before efficacy failure (10.25 hours).

Ethical Considerations

Mr. Carley described EPA's ethics assessment of EMD-003.3 and EMD-004.3. The ethics assessment of these protocols involved review of the revised submissions of February 5, 2007, (reports MRID 47045901 and MRID 47045902), the EPA protocol review of September 15, 2006, and the final report of the October 2006 HSRB meeting (dated January 21, 2007). Applicable ethical standards include 40 CFR §26.1125 (requires prior submission of protocol and supporting materials), 40 CFR §26.1601 (requires HSRB review of protocol and supporting materials), 40 CFR §26.1303 (defines standards for documenting ethical conduct of research), 40 CFR §26.1703 (forbids EPA reliance on research involving intentional exposure of pregnant or nursing women or children), and 40 CFR §26.1705 (forbids EPA reliance on research unless EPA has "adequate information to determine the research was conducted in substantial compliance with subparts A through L").

Deviations from the protocol included commencement of the dosimetry phase before the IIRB approved final changes to the protocol and ICF; this is a potentially serious violation of EPA and IIRB rules, but in this case did not affect the quality of informed consent or subject safety. Data collection also preceded QA review; this was a technical violation without ethical impact. At its October 2006 meeting, the HSRB recommended minor changes including designation of a physician on call and clarification of potential adverse effects in the ICF (for EMD-003.3 only). These changes were not properly implemented before subject consent was obtained for the dosimetry phase. Although the study was conducted with haste and deviations from the protocol were found, the research was substantially compliant with ethical standards; all required documentation is available, and shows no evidence that subjects were misled or endangered by the initiation of the research before IIRB approval of changes suggested by the HSRB. The studies were deemed to be in compliance with all applicable ethics statutes.

Dr. Michael Lebowitz asked whether requiring ticks to cross at least 3 cm into the treated area and requiring at least 2 crossing within a 30-minute time period was standard for tick repellency studies. Mr. Carley answered that this is one of several different ways to test for tick repellency. The time to first confirmed crossing is adapted from time to first bite or FCLIBe, but this concept was not included in the draft guidelines from June 2006. These are the first studies to use this approach in an efficacy test. EPA believes that this is a legitimate way to measure failure of efficacy.

Dr. Fisher inquired whether the withdrawal of half of the subjects from EMD-003.3 before efficacy failure meant only the data from six subjects was analyzed. Mr. Carley responded that the data from all 10 subjects was analyzed. The repellent was effective for more than 10 hours; thus, some subjects needed to leave the test before the first confirmed crossing. The increased efficacy of insect repellents is leading to a need for more sophisticated statistical analysis methods that were not needed when CPTs were in the range of 2 to 3 hours.

Dr. Fisher asked about the rationale for applying the repellent 2 to 3 hours before field testing and whether this was anticipated to mimic consumer use, given that the original protocol called for application at the test site. Dr. Janice Chambers suggested that since the field testing was conducted in November, when the days are short, the repellent may have been applied earlier to permit sufficient time to test efficacy. Dr. Fisher agreed that this may have been an issue, but haste is not a reason to deviate from a protocol presumably designed with scientific rationales. Mr. Carley explained that if early failure of efficacy occurred, the circumstances surrounding any difference in application would be taken into account to determine if deviations from the protocol had an impact. Laboratories that perform repellent work do not have different protocols to use at different times of the year to accommodate mosquito activity and day length. A solution to this problem was to apply the test material immediately before exposure at times of the year during which appropriate mosquito biting activity is found, and earlier if the test is performed at times of less activity. There is little concern that this deviates significantly from typical consumer behavior.

Dr. KyungMann Kim commented that according to the summary of data presented, the statistics calculated were inappropriate; means cannot be calculated if subjects withdraw. Additionally, the data was presented as having no variability; however, variability cannot be estimated if all subjects do not reach failure of efficacy. Although the mean can not be calculated (due to missing data), it is possible to state that the mean is at least 10 hours. However, no determination of variability can be made.

Dr. Fisher asked if the untreated controls also remained in the field for 10 hours. Mr. Carley explained that during the field trials, untreated subjects underwent the same cycles and durations of exposure. Addressing Dr. Kim's comments on the statistical analysis, Mr. Carley reminded Board members that these studies were conducted before the Board's January 2007 discussion on statistical analysis pertaining to such studies; therefore, the studies cannot be expected to be in compliance with the Board's suggestions from the January 2007 meeting. Dr. Kim agreed, but added that EPA's own analysis of the data was troubling.

Public Comments

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

Dr. Carroll thanked the Board for its helpful input and acknowledged the delay between feedback received and the ability to incorporate it into scientific protocols. He explained that the Board would be receiving information on a protocol that, because of EPA scheduling requirements, was submitted before the January 2007 HSRB meeting and thus they could not incorporate Board recommendations. Dr. Carroll commented that he would explain how he will incorporate Board recommendations. For example, after receiving Dr. Kim's advice regarding statistical analysis of the data, Dr. Carroll performed survival analysis on his data; however, the usefulness of this analysis is questionable because EPA is currently developing guidelines for statistical analysis. At present, the data is reported as censored data, which is not a valid approach in Dr. Kim's estimation but does conform to current EPA requirements. Dr. Carroll requested feedback for implementing Dr. Kim's suggestions regarding statistical analysis, particularly in the case of the mosquito repellency testing, because subjects were not bitten. Dr. Kim stated that because none of the 10 subjects received a bite, there is no information with which to estimate time to event. The minimum CPT is greater than 10 hours, but there is no information for statistical analysis, contrary to the results presented by EPA.

Dr. Sean Philpott requested the gender distribution for the completed efficacy studies and whether the control subjects to measure biting pressure were the same subjects at each site. Dr. Carroll agreed to provide this information. Dr. Philpott broached the subject of enrolling subjects using an unapproved revised protocol. The Board recommended, and what is obligatory by IIRB and regulatory statutes, that Dr. Carroll report deviations to the IIRB and develop a plan to correct the deviations. He asked Dr. Carroll to describe progress on this matter. Dr. Carroll explained that he submitted the protocol deviations to the IIRB and discussed them with the director of the IIRB. There is no formal plan to prevent the problem from occurring again, aside from Dr. Carroll's assurance that it would not. He explained that the problem arose in part based on his inexperience with interactions with the IIRB and because the IIRB introduced some errors to the protocol that Dr. Carroll corrected; the IIRB has acknowledged making these errors.

Dr. Fisher commented that although Dr. Carroll has been very responsive to the Board, not all registrants will be as responsive and the Board must be careful not to set precedents regarding its response to deficiencies in protocols. She asked Dr. Carroll to clarify whether the subject pools for the studies overlapped, and if so, whether there is accommodation for variability among subjects, or any other problem arising from subject overlap that the Board should be concerned about. Dr. Carroll answered that there is some overlap among the studies. He stated that there is no reason to believe that there are aberrations among subjects, and in fact it may be best to use the same 10 subjects to allow comparison among studies. He informed the Board that he would be providing a flow chart to track subjects through studies in the future. Dr. Kim commented that for the mosquito repellency test, for the two sites there is overlap of six subjects. If data from the two sites are analyzed separately, this is not a problem, but it could be if the data from both sites are combined.

Dr. William Brimijoin expressed disappointment that the data do not encompass the longest possible protection times. The short days probably are a problem, but so is the high efficacy of the products. He asked whether there was any way to obtain a more accurate CPT. Dr. Carroll acknowledged that he did not anticipate the high degree of efficacy of the products, and that the tests were performed unusually late in the year (which also was a reason for applying the test materials before traveling to the sites). He added that he did not attempt to influence how long subjects remained in the study because the renewed emphasis on subject rights and protection required him to respect the desire of subjects to withdraw. As part of the recruiting process, Dr. Carroll will now inform subjects that the studies could last for more than 12 hours and that the scientific quality of the data relies on subject participation for extended periods of time. Dr. Brimijoin asked whether test material could be applied to subjects 12 hours before traveling to the test site. Dr. Carroll responded that this would result in assumptions and label claims based on data he does not have; however, this approach has been used in the past.

No further public comments were made.

Board Discussion

Scientific Considerations—EMD-003.3

Dr. Chambers opened the science review of EMD-003.3. This protocol tested the active ingredient IR3535 in aerosol form. This protocol was similar to EMD-003.1 and EMD-003.2, previously reviewed by the Board. The product used was produced using Good Manufacturing Practices (GMPs) and experiments performed using Good Laboratory Practices (GLP). Passive dosimetry experiments were recommended and performed; this allowed a 7 percent lower dose to be tested compared to industry standards. Protocol deviations were minor and had no significant effects on the result. Four women and six men served as subjects. Ten subjects were justified as providing adequate statistical power while exposing a small number of subjects to risk. The study found a mean CPT of 10.95 hours $\pm$2.8 hours and mean time to 25 percent failures, adjusted for censoring, of 10.75 hours. These are conservative estimates.

With respect to scientific criteria, existing data was not adequate to test efficacy, thus new studies were required. The benefits of this work include identification of an effective tick repellent with better efficacy and fewer adverse effects. The risks to subjects included irritation from tick bites and exposure to vector-borne diseases, but these risks were minimized because laboratory-reared ticks were used and were removed before biting occurred. Regarding study design criteria, the design was clearly defined and had specific hypotheses. The study involved appropriate controls, dosimetry experiments were performed to quantify dosage, and plans for medical treatment were in place. The results are likely to be generalizable. The subjects were representative of the population, with respect to applicable ethical statutes. The sample did not include vulnerable groups. Measurements were accurate, reliable, and appropriate. Experiments were appropriate and stopping and safety plans were in place. In conclusion, the study is scientifically sound to test the efficacy of IR3535 in an aerosol formulation for tick repellency. Dr. Chambers commended Dr. Carroll for his responsiveness to Board inquiries and the clarity of his data.

Dr. Lebowitz concurred with Dr. Chambers. He found the dosimetry testing to be appropriate and useful. Concerning the efficacy study, withdrawals would be expected in a study lasting more than 12 hours. Comments on conclusions drawn from the data, particularly concerning the Kaplan-Meier survival analysis, are appreciated. He agreed with Dr. Chambers' conclusions regarding sample size. Dr. Lebowitz asked about requiring a second crossing 3 cm or more into the treated area as failure of efficacy, or whether use of one crossing would give a reasonable result. He referred to the table in Figure 19 of the report, which showed that a number of subjects had only one crossing, which would change efficacy results if used as evidence of product failure.

Dr. Kim credited Dr. Carroll for trying a different type of analysis. He continued Dr. Lebowitz's line of questioning regarding the requirement of 2 crossings as product failure. If a consumer receives one bite, the consumer would regard this as product failure.

The definition of CPT in both protocols is unsatisfactory. He asked whether the requirement for more than one bite or crossing was an EPA standard. Mr. Carley responded that current EPA guidelines and drafts of new guidelines require a confirmed bite. The first occurrence of a bite or crossing is historically considered to be anomalous. Requiring a second event to confirm the first has historically been accepted as a test of efficacy failure. Dr. Kim remarked that given the raw data, a different impression of efficacy is gained if the first bite is used as failure of efficacy. He recommended sensitivity analysis to determine which approach was correct. Dr. Gary Chadwick asked whether both analyses could be used. Dr. Chambers remarked that there are existing products that used the second bite or crossing as efficacy failures, and consistency with these products must be maintained. Dr. Fisher commented that using the second bite or crossing is a conservative approach for measuring efficacy, but not consumer protection because it extends the CPT. To a consumer, one bite is one bite and would indicate a lack of efficaciousness. She added that given the apparent lack of attractiveness to mosquitoes of the 10 test subjects, the question is whether the judgments should be conservative in favor of protection or increased efficacy. The EPA may need to change its determination of CPT, relative to the efficacy of the products. Dr. Kim added that the requirement for ticks to cross 3 cm into the treated area also may artificially increase CPT.

Mr. Jordan stated that when EPA discussed the issue of the best way to evaluate efficacy to the SAP, they agreed that there are problems with using the first bite as an indicator of failure. A more reliable basis for assessing failure would be to determine a reduction in the number of bites received; however, this requires subjects to be bitten numerous times and compare the number of bites received by treated versus untreated subjects. Because of scientific and ethical concerns, this approach was not used; instead, efficacy failure was used to determine CPT. EPA is mindful of the biological uncertainty of a single bite and thus requires confirmation of the first bite with a second bite. EPA also acknowledges the high degree of variability in the population regarding attractiveness to mosquitoes and how a repellent works for a given person. The CPTs indicated on labels are for informing about the relative benefits of different products, not to guarantee a specific CPT.

Dr. Lebowitz commented that, given individual variability, the large numbers of withdrawals, and the requirement for multiple crossings or bites, a solution to this problem

would be to significantly increase sample size to have sufficient observations to satisfy crossing requirements and overcome variability issues. Dr. Brimijoin reminded him that the HSRB's mandate is to ensure protection of research subjects, not protection of the public. The Board recognizes the conflict between assuring good science and minimizing risk to subjects. The best science requires many more subjects, and would require more mosquito bites, but this would significantly increase the risk to subjects. Dr. Brimijoin stated that he would prefer a larger sample size because he believes the risks of these experiments are low, but EPA standards require minimization of subject exposure.

Dr. Brimijoin also stated that although it is appropriate for the Board to ask questions outside its realm of expertise and it is legitimate to question methods that are standard in the field, the Board must recognize existing standards and why they exist. For example, use of the confirmed bite standard might reduce noise in the data. Dr. Fisher agreed that although the Board must consider the value of the knowledge produced for public protection, the Board must focus primarily on subject risk. Regarding relative efficacy, Dr. Fisher commented that consumers may rely on the 10+ hour CPT to know when the product would need to be re-applied.

Regarding Dr. Carroll's method as a resolution between other methods, Mr. Carley stated that using LIBes would have no affect on design, and, in Dr. Carroll's view, an actual bite is not needed to confirm failure; others in the field disagree.

Ethical Considerations—EMD-003.3

Dr. Philpott opened the ethics review by agreeing with the ethical strengths and weaknesses of EMD-003.3 as detailed by Mr. Carley. It is clear that the likely societal benefits of this study justify the potential risks, which are minimal because IR3535 has been commercially available for a number of years. Participants also are unlikely to be at risk for vector-borne diseases from exposure to the laboratory-raised, pathogen-free ticks. Clear stopping rules and medical management plans are in place. The protocol has procedures to minimize coercion during the recruitment process. Compensation for participation is reasonable, and children and pregnant women are excluded from the study. Because of potential stigmatization for exclusion, Dr. Carroll has developed a well-designed approach to ensure confidentiality. In general, the study comports with the applicable requirements of 40 CFR 26, subparts K and L. There is no evidence that the conduct of this research was unethical.

As noted previously, some serious deviations from accepted practices occurred, namely using an unapproved ICF containing handwritten changes during recruitment. Dr. Philpott commended Dr. Carroll for reporting this deviation to the IIRB. Drs. Richard Sharp and Jerry Menikoff agreed with Dr. Philpott's assessment and had no further comments.

Dr. Fisher concluded that the Board recommends that the data from this study can be used by EPA. She commended Dr. Carroll for his clarity, GLPs, and performing the dosimetry phase of the study. The Board recognized problems with generalizability of the results, but believed Dr. Carroll has justification for the small sample size. The reasons for performing this

study are sound (lack of efficacy data on this formulation, potential societal benefit, and low risk to subjects). The deviations from the protocol do not affect the data.

The Board questioned the use of the second crossing to determine loss of efficacy, but realizes this does not affect this study; however, the Board recommended that this should be a matter for future consideration by EPA. There also were questions concerning comparing the amounts of IR3535 used in the dosimetry phase to toxic benchmarks. Regarding ethics, there is minimal risk to the subjects because of the use of pathogen-free ticks and removal of ticks before biting occurs. The Board reviewed the deviations that occurred and appreciated Dr. Carroll's responsiveness to this issue and his willingness to work with the IIRB.

Scientific Considerations—EMD-004.3

Dr. Chambers opened the science review of EMD-004.3. This protocol tested the efficacy of IR3535 in aerosol formulation against mosquitoes in two field settings (marsh/grassland and forest/flooded marsh). An alternate site was used as the second test site because of insufficient biting pressure at the initial site. There was no evidence of West Nile Virus (WNV) or other vector-borne diseases at either site. Ten subjects were tested at each site, and untreated controls also were tested to determine mosquito biting pressure. The trial terminated after dark and results allowed only a minimum performance (CPT) to be determined, thus statistical analysis of variance was not possible. The scientific justification for this study was the same as that for EMD-003.3. In conclusion, the report on EMD-004.3 contains data that are sufficiently sound to assess mosquito repellent efficacy of the aerosol formulation of IR3535.

Dr. Brimijoin agreed with Dr. Chambers' assessment of EMD-004.3 and recognized the same issues surrounding statistical analysis of the data. Dr. Kim asked if there have been previous efforts to understand the potency of the different preparations of IR3535. He commented that the aerosol formulation appeared to be more potent against mosquito biting compared to the results for the lotion and pump spray formulations. Dr. Fisher agreed that the aerosol formulation appeared to be more potent and asked whether it was typical that aerosols are more effective. She also asked whether perhaps the mosquitoes exhibited different behavior in this study. Dr. Chambers said that, in her opinion, questions on comparison of formulations were beyond the purview of the Board and added that biting pressure was adequate based on data from the controls. Dr. Brimijoin agreed that data from the control subjects showed that there was substantial biting pressure at the site; therefore, failure to bite is a treatment effect. This effect would be more obvious if the study had enrolled more controls, but this was not possible for ethical reasons.

Ethical Considerations—EMD-004.3

Dr. Philpott opened the ethics review of EMD-004.3. The process for subject enrollment and maintenance of confidentiality was the same as for EMD-003.3. EMD-004.3 had a larger number of subjects because testing was conducted at two field sites, although there was overlap among some of the subjects at each site. The two control subjects used to determine biting pressure were experienced laboratory personnel. The study enrolled 26 to 28 volunteers,

including alternative subjects to replace any subjects who withdrew or were unable to participate; this approach helped protect subject confidentiality.

EMD-004.3 presented some distinct concerns, namely the risk of disease from infected mosquitoes. Appropriate efforts were made to minimize risk. The studies were intended to be conducted in areas in which arthropod-borne diseases had not been detected by vector control agencies for at least one month prior to the study. This precaution was violated by the detection of WNV in a sentinel chicken prior to the study. The study proceeded because vector control agencies concluded that there was no further disease activity at the site.

Other ethical issues included the use of an unapproved ICF. Additionally, the untreated controls may not have received sufficiently explicit descriptions of the risk. Dr. Sharp asked whether, given the protocol violations described by Dr. Philpott, this protocol could be deemed to be in substantial compliance with ethics statutes. Dr. Menikoff reminded Dr. Sharp that the Board must be consistent with the meaning of "compliant" as determined during the January 2007 HSRB meeting. Dr. Fisher agreed, and noted that further discussion of the meaning of "compliant" would take place later in the meeting. She agreed that the Board should consider whether these protocol violations were substantial deviations from ethical standards, and asked whether subjects were informed of the issue with the informed consent documents. Mr. Carley responded that subjects participating in the dosimetry phase signed the September 2006 version of the ICF that Dr. Carroll had amended in writing to reflect HSRB suggestions. The final changed version was approved on November 1, 2006, and was used to consent subjects for the efficacy phases of both the tick and mosquito studies.

Dr. Fisher inquired whether subjects had been informed about the detection of WNV in a sentinel chicken. Dr. Carroll answered that he noted this information in his report, but the chicken in question was not part of the flock closest to the site. Instead this flock was far enough from the site (approximately 30 miles) that its presence was not considered a violation of the protocol. Dr. Philpott expressed concern that the term "regions," as used in the ICF, to inform participants about the possible presence of vector-borne disease is too vague. If the flock is in the same county as the test site, it could be considered to be in the same region, and thus proceeding with the study was a violation. Dr. Carroll should remember this when planning similar protocols that use this approach for minimizing exposure to vector-borne diseases. Dr. Carroll also should consider analyzing mosquitoes caught at the test site. Dr. Fisher added that at the April meeting approving the January report the Board recommended that, for future protocols, if the region tested is not pathogen-free for 30 days, post-study testing of trapped mosquitoes should be performed.

Dr. Fisher concluded that the Board comments indicated the EMD-004.3 is a valid study, regardless of issues with interpretation and analysis of the data. CPT could be related as at least 10 hours, rather than 10 or more hours, in accordance with available data. There were some issues concerning the ICFs and the extent to which the study followed some requirements. The Board's consensus was to approve this study.

Carroll-Loye Mosquito Repellent Efficacy Protocol WPC-001

Introduction

Mr. Carley provided background on a proposal for a field test of mosquito repellency for a conditionally registered formulation containing Oil of Lemon Eucalyptus (OLE) as its active ingredient. Conditional registration means that EPA has the authority to approve products similar to previously approved products when fewer than all registration requirements have been satisfied; the unaddressed requirements are made conditions of registration that must be resolved within a specific timeframe. This product was registered with specific requirements to conduct product-specific studies. OLE is used in other similar products at ranges encompassing that used in this product. The protocol WPC-001 is adapted from and closely similar to Carroll-Loye protocols EMD-004 and SCI-001, previously reviewed favorably by the HSRB. The few remaining deficiencies in this protocol can be easily corrected and thus EPA believes this protocol is ready for HSRB review.

Scientific Considerations

Dr. Fuentes presented the scientific considerations for protocol WPC-001. The objectives of this study were to test the mosquito repellent efficacy characteristics of the test material and to satisfy a condition of registration imposed by EPA. The test material, Repel 30 LE (EPA Reg. No. 305-62), contains 30 percent OLE in a pump spray formulation. The oral Lethal Dose (LD)-50 is less than 5,000 milligrams per kilogram (mg/kg) and the dermal LD-50 is greater than 2,000 mg/kg.

The study includes a dosimetry phase with 10 subjects, to establish the typical consumer dose for use in efficacy testing. Subjects are trained in the laboratory to aspirate landing mosquitoes before they bite, using laboratory-reared, pathogen-free mosquitoes. Because there is only one treatment, the study is not blinded. The study involves two field trials, each enrolling ten treated subjects and two untreated "experienced" control subjects. Untreated subjects are included to monitor biting pressure; each will be attended by two assistants to aspirate mosquitoes before they can probe or bite. Both treated and untreated subjects are exposed to mosquitoes for 1 minute every 15 minutes. Product efficacy is measured as average time from treatment to FCLIBe.

The field sites are described in the report as the California Central Valley or Florida Keys, depending on the season. Expected wild mosquito populations include *Aedes vexans*, *Ochlerotatus melanimon*, *O. taeniorhynchus*, and *Culex pipens*. Variables, including biting pressure (threshold = 1 LIBe/minute), FCLIBe, and time to FCLIBe, will be measured. Test results will be analyzed by calculating the mean time to first confirmed LIBe; untreated controls are not used for comparison of treatment means. Means will be reported with 95 percent confidence interval of the mean and associated standard deviation; other analyses may be used as appropriate to the results.

The sample size reflects a compromise between financial and ethical concerns. Sample size is difficult to predetermine without knowing the distribution of outcome values. EPA

guidelines recommend six replicates, which has been widely regarded as sufficient to show statistical significance at $P<0.05$; 10 replicates slightly improves accuracy in estimating the population mean.

Necessary protocol revisions include deletion of the reference in §6.2.1 to untreated controls for the dosimetry assay; provision in the statistical plan for diagnostic statistical tests for normality, and for analysis of non-normally distributed data; inclusion of roughly equal proportions of male and female subjects in the sample; and inclusion in limb surface areas measuring procedures for recording the exact locations of the four measured circumferences, so that dosimeters can be placed at the same locations.

If further revised as suggested, this protocol is likely to comply with scientific standards and yield scientifically reliable information because it would produce important information that cannot be obtained except by research with human subjects and it has clear scientific objectives; the study design should produce adequate data to achieve those objectives.

Ethical Considerations

Mr. Carley presented ethical considerations for WPC-001. The proposed study would field test the mosquito repellent efficacy of a single test formulation, containing OLE as its active ingredient. The test formulation was conditionally registered with claims for "up to 6 hours" of protection; EPA requires product-specific efficacy testing to maintain the product's registration. The proposed study presents value to society by making available a potentially attractive alternative to other available repellents, some of which are found unpleasant by many users.

Subjects will be recruited among "communities of friends, neighbors and scientists" near the investigator's laboratory. Exclusion factors are students or employees of the investigator; children, or pregnant or nursing women; those sensitive to repellents or to mosquito bites; those in poor health or physical condition; and those unable to speak and understand English. No subjects come from vulnerable populations. More detail is needed about recruitment of the two "experienced" subjects who will serve as untreated controls.

Risks include irritation of the eyes on contact with the repellent, the repellent is harmful if swallowed, and possible exposure to biting arthropods and/or arthropod-borne diseases. Risk minimization procedures specific to the repellent include exclusion of sensitive candidates, closely monitoring use of the repellent during the dosimetry phase, and having a technician apply the repellent. Risks from mosquito bites are minimized by excluding sensitive candidates, training subjects to aspirate mosquitoes before they have time to bite, and minimizing exposure of skin. Risks of disease are minimized by conducting research where no mosquito-borne viruses have been detected for at least a month, and by minimizing bites. The probability of risks is characterized as "extremely small" because of the low acute and chronic hazard profile of the product (although the product is a Toxicity Category II eye irritant), design of the research to minimize exposures, training subjects to aspirate landing mosquitoes before they have time to probe or bite, and performing field testing in areas free of WNV. An additional way to reduce risk would be to perform post-study serological testing of mosquitoes caught at the test site.

Regarding benefits, there are no direct benefits to subjects; the primary direct beneficiary is the sponsor. If the material is proven effective, indirect beneficiaries will include repellent users who prefer this product to other repellents. No reasonable opportunities have been overlooked to further reduce risk while maintaining scientific robustness; the residual risks to subjects are very low and are reasonable given the expected societal benefits to repellent users, which are likely to be realized.

The IIRB of Plantation, Florida reviewed and approved the protocol and informed consent materials on January 23, 2007. This IIRB is independent of the sponsors and investigators and is registered with the Office for Human Research Protections (OHRP). It is not accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP) or any other accrediting organization as far as EPA can determine. EPA has determined that this IIRB's procedures meet regulatory standards.

Regarding the informed consent process, the description of subject recruiting and consent processes in California is complete and satisfactory; however, more detail is needed regarding the recruiting process in Florida, especially concerning the role of the Mosquito Control District administration. The IIRB-approved ICF is appropriate for both treated and untreated subjects and is included in the protocol, but misleadingly suggests the test material is not yet registered with EPA.

The protocol shows adequate respect for subjects through the methods proposed for managing information about prospective and enrolled subjects that will generally protect their privacy; however, subject privacy would be better protected if subject names did not appear on data collection forms. Subjects will be free to withdraw at any time, and will be reminded of this at several points. Medical care for research-related injuries will be provided at no cost to the subjects.

This is a proposal for third-party research involving intentional exposure of human subjects to a pesticide, with the intention of submitting the resulting data to EPA under the pesticide laws. The primary ethical standards applicable to this research are 40 CFR 26, subparts K and L. A point-by-point evaluation of how this protocol addresses the requirements of 40 CFR 26 subparts K and L and the additional criteria recommended by the HSRB appears as Attachment 1 to the EPA Review.

Required revisions to this protocol include a description of how untreated controls will be recruited, and how the process of informing them will differ from that used for treated subjects. It will also include a detailed description of the recruiting process in Florida equivalent to that used to describe the process used in California, with particular attention to the role of the Mosquito Control District administration.

Regarding the status of protocol WPC-001's compliance with ethical standards, all requirements of §26.1111, §26.1116, and §26.1117 are met; with requested revisions, all requirements of §26.1125 are met; all requirements of §26.1203 are met; all elements of National Academy of Science (NAS) recommendation 5-1 are satisfied; and all elements of NAS

recommendation 5-2 are satisfied. If further revised as suggested, protocol WPC-001 will meet the applicable requirements of 40 CFR 26, subpart K and L.

Dr. Fisher inquired whether FCLIBe was the same as first confirmed crossing. Mr. Carley explained that this was the equivalent of crossing. For EMD-004.3, the endpoint for failure of efficacy was the average time from treatment to the FCLIBe. Efficacy failure is measured as the FCLIBe confirmed by another crossing within 30 minutes; CPT is measured as time to efficacy failure. Dr. Fisher asked whether data on "rejected" bites are collected. Mr. Carley responded that it is collected as raw data. An entry is made for every 15 minute time period to record the numbers of LIBes. Thus, unconfirmed landings are recorded, but are not counted if a subsequent landing does not occur within 30 minutes. Dr. Fisher asked whether EPA could modify the way it determines FCLIBe. Mr. Carley answered that EPA could perform parallel analyses (using first landing versus first confirmed landing) for this study, but data from previous studies from which to do this sort of analysis would not be available. Dr. Fisher asked whether the Board should recommend that other investigators record data this way to allow for other analyses in the future. Mr. Carley responded that the Board may want to discuss this issue at the June 2007 meeting after they review a similar protocol from another investigator.

Dr. Kannan Krishnan asked whether Repel 30 LE is registered. Mr. Carley answered that the product is conditionally registered. Dr. Krishnan inquired about the concentration of the active ingredient in Repel 30 LE. Mr. Carley responded that this product has, at 30 percent OLE, a lower concentration of OLE than in previously registered pump spray products also containing OLE. A higher concentration product is registered with no conditions. Repel 30 LE is conditionally registered because data from product-specific test conditions was not available. Dr. Krishnan questioned whether there was any concern about changing the composition or the vehicle of the product. Mr. Carley replied that the product is similar enough to other products on the market to be considered safe. The product has already met a number of conditions and the remaining questions strictly concern efficacy. The results of this study will be used to modify label claims. Dr. Krishnan questioned whether EPA has supporting data on file concerning the toxicity class of the product. Mr. Carley explained that EPA has data covering other product requirements, including chemical and toxicity data.

Dr. Sharp requested clarification of the recommendation for revision of the recruitment procedure for untreated controls and whether EPA was asking for details beyond those provided to the Board. Mr. Carley explained that EPA wanted further detail on the process for soliciting interested subjects, the process by which the investigators will apply subject criteria, and how subjects will be offered the chance to serve as untreated controls.

Public Comments

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

Dr. Carroll addressed questions concerning the subject recruitment process, including subject influence on repellent performance, how subjects may differ with respect to mosquito attractiveness, and how study developers consider who might participate in the trial.

Although it is known that gender has a strong influence on mosquito attractiveness, most studies are inconclusive regarding whether men or women are more attractive to mosquitoes. Thus, a gender balance generally is used for mosquito repellency studies. Regarding the sampling frame for this study, comparison of the Carroll-Loye Biological Research volunteer database to Davis, California, census data shows a similar ethnic distribution. Most individuals in the volunteer database are between 20 and 40 years of age, with a smaller number between 40 and 55 years of age. The individuals are relatively young, well-educated, and likely to be life science researchers or students. The subjects show substantial interest in participating, but this is not likely to influence results of the study. Carroll-Loye Biological Research investigators do not actively or directly encourage participation; instead, individuals in the database have requested that investigators contact them when test subjects are needed. Persons who will serve as untreated control subjects are limited to experienced technical personnel, who are screened with the same exclusion criteria as are other subjects, and have additional inclusion requirements.

Dr. Carroll requested comments from the Board regarding language on the ICF for informing untreated controls. He presented his proposed language, and added that he would like to use only one ICF for both treated and untreated subjects. He also asked whether the Board recommend that he perform sampling for diseased organisms during testing. California has an intensive disease-sampling program and California vector ecologists suggest a 2-week buffer to ensure the absence of vector-borne diseases.

Dr. Fisher requested Dr. Carroll explain the size of the "region" as described in the study protocol. She said that the testing criteria would be determined by the extent to which Dr. Carroll can ascertain that there was no evidence of disease in a region relevant to the test site for the past 30 days. Dr. Carroll asked the Board to consider in its discussion of this protocol how data from mosquito sampling would be used.

Dr. Philpott inquired whether the recruitment protocol shown to the Board was similar to the previous one described for testing at the Florida site. He expressed concern that flying study subjects from California to the Florida site would represent undue inducement to participate. Dr. Carroll answered that the Florida recruitment process was still being developed; protocol WPC-001 does not include testing in Florida. Dr. Fisher questioned EPA as to why the Board was reviewing a protocol that appeared to be somewhat undeveloped. Mr. Carley responded that his concerns about the inadequate description of the Florida recruitment procedure could be alleviated by deletion of the reference to recruiting in Florida; Dr. Carroll informed the Board that this protocol will be performed only in California. Dr. Sharp added that, in his opinion, the protocol is well-developed aside from the gap in the Florida recruitment process.

Dr. Fisher requested clarification concerning the implications of season or temperature on the effectiveness of products tested in mosquito repellency field studies, and whether this would influence the need for untreated controls. Dr. Fuentes explained that season and temperature influence the ability to locate mosquitoes. The activity of the product does not change, but the numbers and types of mosquitoes at a given site do. The control group provides information on this by providing a measure of biting pressure. If biting pressure is adequate, any difference in the amount of bites received by controls compared to treated subjects is a treatment effect.

Dr. Fisher asked whether a control is compared to a treated subject at each of the described 15-minutes intervals. Mr. Carley responded that data concerning mosquito landings is collected for controls at the same intervals and for the same duration as treated subjects.

Board Discussion

Scientific Considerations—WPC-001

Dr. Krishnan questioned why, given that EPA has sufficient data on the safety of this product, human studies were required and justified. He added that although most of the essential elements for the protocol have been adequately described and are appropriate, he has concerns regarding sample size and statistical analysis. The sample size justification is not convincing. Dr. Krishnan commented that he had hoped the results of the completed mosquito repellent efficacy studies could be used to inform sample size for this study. Given the concerns of Drs. Alicia Carriquiry and Kim regarding the confounding of CPT calculations by subject withdrawal, perhaps guidelines need to be established concerning how long subjects are required to remain in the study. Dr. Krishnan added that once dosimetry studies are complete, the dose should be compared to a toxic benchmark.

Dr. Krishnan concluded that based on the available information, this protocol can provide scientifically reliable data. The protocol approval is based only on activities in California, not for the Florida site. The investigators also should address issues pertaining to statistical analysis, which should help obtain more reliable results.

Dr. Fisher related comments from Dr. Carriquiry regarding protocol WPC-001. Dr. Carriquiry noted a great deal of variability in the dosimetry phase of previous studies, and asked if, given the variability of consumer use, should more than one dose level be tested to obtain data that are more meaningful for the consumer. Mr. Carley responded that EPA has accepted a single dose for as long as it has required and reviewed such studies. For most studies, the dose used is based on a "rule of thumb" not on actual measurements. At the last HSRB meeting, the Board asked EPA to consider best methods for dose studies; EPA is considering this but has not yet developed a consensus. Dr. Lebowitz reminded the Board that it had indicated satisfaction with single dose protocols reviewed during the morning session of this meeting. He expressed dissatisfaction with the use of a single dose because of inter- and intra-individual variation, but recognized that adjusting sample size could resolve these issues and permit use of a single dose. Dr. Kim questioned whether the dose used was close to that expected to be used by the consumer. Mr. Carley explained that labels for repellents usually informed consumers to "apply for full coverage." Consumers tend to re-apply product if they are bitten. Regardless of better ways to cope with the variability inherent in this work, EPA is not trying to produce an accurate prediction of CPT for each user. CPT is used for comparison with products currently on the market; these are not dose-response studies.

Dr. Brimijoin inquired whether, given the numbers of different investigators performing these studies, data from different studies are truly comparable. Dr. Fisher added that she was surprised these studies are not more informative concerning the duration of these products' effectiveness. Relative efficacy cannot be compared because the studies are performed under

different conditions, with different subjects, and at different sites. Dr. Chambers reminded Board members that these are field studies, which will not be as clean as those performed in a laboratory setting. The studies do provide consumers with information that will help them choose which product to use. Using multiple doses in a study would require more subjects and thus increase risk.

Dr. Carriquiry commented that there was no discussion in the protocol of how CPT is determined if a subject withdraws before FCLIBe. She asked whether a power analysis had been performed to determine the number of subjects needed to show that any effect is not due to chance. These calculations typically rely on previous study results. She asked whether the Board has given appropriate guidance for justification of sample size. Dr. Kim answered that the studies were essentially descriptive and P-values cannot be appropriately calculated for them. Dr. Fisher agreed that the Board had concerns about determining sample size. Mr. Carley explained that EPA is considering this issue, but at present, the sample size of 10 is acceptable. It is the responsibility of EPA, not individual investigators, to address general questions concerning EPA guidelines and standards and how to use results to determine label language. Mr. Jordan agreed with Mr. Carley, and added that Dr. Kim's comments are helpful for describing the purpose of including more subjects to give more precision to estimates of CPT. Investigators provide data for EPA use; EPA must decide how much precision is required in this data to make label claims for products. These issues are broad and cut across many fields, and will be used by EPA to consider and perhaps revise its guidelines. Transitioning from old to new guidelines also will require planning. The current rule of thumb used by EPA, and the onus on investigators, is to determine whether the current studies are as good as or better than previous studies. Dr. Fisher agreed, but added that the Board questions if changes can be made at the present to achieve standards the Board believes are necessary. The Board believed EPA must address these issues. Mr. Carley reminded the Board that these protocols represent regulatory science and regulatory standards. Guidelines for these studies must be consistent; a compromise must be reached between refining the guidelines at every HSRB meeting and accepting protocols because they follow historical, albeit perhaps less than optimal, standards.

Dr. Brimijoin commented that it appeared that similar studies are being held to progressively more rigorous standards. This could be unnerving to proponents, but the Board should continue to push for higher standards, particularly if a given analysis is inappropriate or there is an easy way to resolve an issue. Dr. Kim acknowledged the obvious level of frustration given that several of the Board's recommendations have not been implemented as the Board would like. EPA does not provide clear input to registrants (concerning sample size, CPT derivation, etc.) and thus it may not be realistic to see changes in the protocols reflecting the Board's advice. It is also clear that any change implemented will have considerable and broad implications, given EPA's historical body of data. Nonetheless, the Board must continue to push for better science, and especially must address any "fatal flaws" it discovers. Mr. Carley clarified that Dr. Kim's concerns had not been implemented in the protocol reviewed at this meeting since the protocol was written before the January 2007 HSRB meeting. EPA will develop guidelines based on Board suggestions and disseminate the guidelines to investigators. Dr. Chambers suggested that EPA provide the Board with background about EPA data sets and regulatory constructs to help inform the Board about insect repellents and regulations.

Mr. Jordan agreed that this would be helpful and said he would try to provide such materials for Board review of the occupational handler exposure studies.

Ethical Considerations—WPC-001

Dr. Sharp opened discussion on ethical considerations for WPC-001. He thanked Mr. Carley for his thorough review of this protocol. The social benefits for this study are well articulated. OLE is an important alternative repellent, especially for those sensitive to the smell of other commercially available mosquito repellents. The limited risks inherent to this study were minimized appropriately. Dr. Sharp commended Dr. Carroll on the improvements Dr. Carroll made to the protocol. Recruitment in Florida could be a serious issue because there was little definition of recruitment procedures to be used in that state. However, because the study will be conducted in California, removal of references to recruitment in Florida could be removed from the protocol. In conclusion, this protocol, with minor revisions, meets the applicable ethical requirements.

Dr. Menikoff agreed with Dr. Sharp's assessment. He expressed concern that there was not a separate ICF for control subjects. Control subjects face higher risks than treated subjects and one ICF that does not indicate whether the risks detailed are for treated subjects or control subjects may not permit control subjects to recognize that they are at higher risk. An addendum should be made that control subjects signature could be added to the ICF to ensure control subjects are properly consented. Dr. Susan Fish agreed with Drs. Menikoff's and Sharp's assessments.

Concerning the ICF, Dr. Sharp questioned whether the Board wanted to substantially change an ICF that had been reviewed and approved by an IIRB, suggesting the Board should defer somewhat to the IIRB's assessment. Dr. Gary Chadwick agreed, but maintained that whether people have the information necessary to make an informed choice is a significant ethical issue. The Board recommended that this issue be addressed. Dr. Fisher agreed that it was a significant issue and that the ICF did not distinguish between control and treated subjects. Mr. Carley explained that part of the confusion surrounding this issue arose from inclusion of the Florida site in the protocol reviewed by EPA and the Board. Dr. Carroll currently does not plan to conduct the study in Florida, so issues surrounding recruitment in Florida may be solved by reorganizing the protocol.

Dr. Fisher concluded that the Board found the protocol to meet scientific criteria. Concerning ethics, she agreed that subjects' names should not be included on data forms, the ICFs need to be finalized, and a clearer determination of how control subjects are recruited and selected was needed. The protocol also should clarify that the study will not be performed in Florida.

Research Conducted After April 7, 2006: Meaning of "Substantial Compliance" with 40 CFR Part 26

Mr. Jordan presented EPA considerations on the meaning of "Substantial Compliance" in 40 CFR §26.1705. EPA has prohibited reliance on unethical human research with non-pregnant,

non-nursing adults conducted after April 7, 2006, unless EPA has adequate information to determine the research was conducted in substantial compliance with subparts A through L of this statute. Without adequate information, EPA cannot make a determination of compliance. An exception to this rule is that if EPA has data that do not meet ethical standards, the data may be used to support regulatory action leading to more stringent health protection or improved public health

This rule was developed from NAS recommendations for "intentional human dosage studies" (NAS Recommendation 5-6). The recommendation was modified slightly to clarify that EPA would consider refusing to rely on a completed human study only if the study fails to "substantially" comply with the applicable ethical standard. This addition reflects EPA's judgment that relatively minor administrative or record-keeping deficiencies in a researcher's compliance with a rule as complex as the Common Rule would not in themselves justify rejecting otherwise scientifically valuable and ethically conducted research.

The information contained within the presentation, "Compliance Oversight in Human Subjects Protection" by Dr. Kristina C. Borror, Director of Division of Compliance Oversight in Office of Human Research Protection (OHRP), Department of Health and Human Services (DHHS) (February 1, 2005) also informed EPA's decision. This report demonstrates that deficiencies often occur in research involving human subjects, but most are not serious. The report describes 269 determination letters sent over a period of 4 years to more than 180 institutions. Most letters were based on review of submitted documents, although OHRP also conducted site visits at 18 institutions. Within the 269 letters were 71,000 citations for non-compliance (approximately four citations per letter); 142 institutions had at least one citation; the median was four citations per institution. During this time, OHRP suspended or restricted assurances for only 20 institutions, indicating that only 20 institutions had serious or numerous deficiencies. This suggests a gradient in terms of the seriousness of the citations, although the report does not contain detailed information concerning the kind of violations cited. Approximately 51 percent of all institutions cited had deficiencies in IIRB documentation for informed consent processes, although most of these deficiencies were not serious.

Public comment was permitted when EPA was in the final phases of developing this regulation, and most comments indicated a lack of clarity concerning the definition of key phrases (i.e., "fundamentally unethical," "significantly deficient," or "substantial compliance"). Overall, although most investigators wanted EPA to specifically state the number or types of comments that would lead to a study being deemed "not in substantial compliance," EPA believed this was unnecessary. EPA agreed with NAS that each study would require case-by-case evaluation. EPA also expected the terms to develop greater clarity over time, through HSRB and public review of EPA decisions concerning this matter.

The term "substantial compliance" has legal meaning and the phrase appears in judicial review, often in disputes between two parties when trying to determine if the complaining party's requests were met as detailed in a contract or in support of whether a regulation was met. The term involves interpretation of the underlying intent of a requirement and allows flexibility in judging the acceptability of behavior. For example, the way in which the HSRB approached

review of several insect repellent studies in January 2007 reflected good and thoughtful judgment concerning substantial compliance of the protocols with ethical standards.

EPA recommended that the Board not attempt to define *a priori* standards for "substantial compliance" but instead build a record of specific decisions taking into account such factors as the nature and number of deficiencies, the investigator's intent, any relevant past conduct, prevailing practices in the field, and the likely significance of the deficiency for subjects of the research. The Board is also asked to explain the reasoning regarding any HSRB conclusions concerning whether compliance is "substantial."

Dr. Chadwick discussed the definition of "substantial compliance." He commended EPA's approach to soliciting HSRB input. He cautioned Board members to be sure to understand the difference between ethical deficiencies and regulatory deficiencies. Dr. Chadwick added that it is unrealistic for the Board to determine an investigator's intent, and also may be unrealistic for the Board to determine and consider an investigator's past conduct. Dr. Philpott agreed that determining intent probably is not possible. Dr. Fisher agreed that the Board should avoid assessing intent, because intent is not provable. EPA can consider intent or relevant past conduct if it chooses, but the Board determines only if regulations were followed and if not, were these lapses likely to cause harm or violate subjects' rights. The phrase "substantial compliance" is contradictory because it implies that following all regulations is not necessary. Regarding consideration of relevant past conduct, Dr. Fisher stated that, at some point, sponsors should be expected to be cognizant of applicable regulations and able to develop solid ICFs. The Board must consider precedent; behaviors that may be acceptable now may not be acceptable in the future.

Dr. Lebowitz stated that the presentation provided legal definitions of key terms. The Board assesses whether a protocol is sufficiently scientifically and ethically sound. He expressed doubt considering whether the Board ever used the term "substantial compliance." An education process may be necessary for the Board to be able to define "substantial compliance." Dr. Menikoff stated that he found the criteria useful. Intent cannot be directly measured, but assessing the conduct of an investigator provides reasonable information concerning what the investigator intended to do. Problems with ICFs are usually minor mistakes, such as typographical or version errors; in these cases, the intent of the investigator was to comply with ICF guidelines. Past conduct also can offer clues concerning intent. Dr. Brimijoin agreed that EPA has taken a sensible approach to this issue. It is unlikely the Board will ever see a perfect protocol; it may have to make judgments that a protocol is "close enough" to compliant. EPA consults the Board on whether it considers a protocol to be in substantial compliance, but EPA makes the final decision regarding this issue.

Dr. Richard Fenske requested to see the report discussed in the OHRP presentation, if such a report exists. He expressed discomfort with the legal framework of the guidelines. For example, identification of a "complaining party" would be unclear for most scientific protocols. A legal context may not be appropriate for a science and ethics advisory board. Overall, however, Dr. Fenske found the recommendations helpful (especially those concerning the nature and number of deficiencies and the likely significance of the deficiency for research subjects), although the other suggestions could be amended. He commented that the Board acknowledges

that errors, such as using the wrong version of an ICF, may occur in field studies, which speaks to the intent and past performance of the investigator. He also recommended that EPA inform the Board about investigators' past performance when possible.

Dr. Fisher remarked that there may be differences in "substantial compliance" when the Board is reviewing a proposed protocol compared to a completed protocol. If the HSRB makes recommendations concerning compliance for a proposed protocol, the investigator should incorporate the recommended changes. The HSRB never concludes that it is permissible for an investigator to disregard its recommendations. Mr. Jordan clarified that this rule applies only for EPA use of data from a completed protocol. Dr. Fisher agreed that when the Board reviews a completed protocol, it can determine only the extent to which the investigators followed the regulations and whether any deficiencies resulted in harm to the research subjects. She expressed concern about using "intent" to decide compliance. Additionally, past conduct often is not admissible in legal situations. The Board can evaluate only how a protocol was conducted, if it was in compliance with regulations, and if it violated human subject rights. Dr. Chadwick remarked that the Board must understand that no protocol will be 100 percent correct. There needs to be allowances for accepting data from studies with minor deficiencies. Dr. Menikoff agreed that few protocols would meet all requirements and regulations, and intent should be considered. He cited as an example Dr. Carroll's additional language to the ICF, which was technically in violation of regulations, but resulted in a better, more informative ICF. Dr. Fisher stated that the Board did not know Dr. Carroll's intent, but only found that the changes did not violate subject rights or result in less information for subjects. Dr. Chadwick stated that although he agrees with the idea of flexibility, the HSRB is not in a position to decide or comment on intent.

Dr. Sharp also cited Dr. Carroll's situation, stating that the Board knew there was a consent violation and proceeded to obtain information that allowed it to determine this was an honest mistake and not a protocol violation. Dr. Fisher responded that if the change to the ICF had not provided sufficient protection, the HSRB would judge it to be unethical. Intent should not be considered in the Board's assessment. Dr. Sharp reminded Dr. Fisher that this rule applied to previously conducted studies, and the Board would be determining only if the data was usable by EPA. Dr. Philpott agreed with Dr. Fisher that determining intent was not possible. Mr. Jordan agreed that it could be difficult to infer intent, but still may be worth pursuing. Concerning Dr. Sharp's point that this consideration applied only to previously conducted studies, Mr. Jordan explained that EPA's goal for these assessments is to try to prevent violations from occurring in the future. Having an understanding of an investigator's motives or intent that lead to deficiencies is relevant for predicting the type of response from EPA that will lead to a change in behavior. He clarified that EPA operates in a regulatory context, and appreciates the clarification of deficiencies as regulatory rather than ethical. The intent underlying the regulations is to ensure ethical treatment of human subjects, thus, it is relevant to try to understand the ethical impact of a regulatory deficiency. The most powerful response EPA has to address deficiencies is to inform a sponsor that their data are unusable and they will have to repeat the study, leading to added expenses and delays for the sponsor. EPA also can impose civil or criminal penalties, report an investigator to OHRP, or disqualify an investigator from receiving EPA grants. The choice of which measure to use depends in part on how effective the measure will be in changing behavior to avoid repetition of a mistake.

Dr. Brimijoin suggested that the Board not think of EPA's recommendations for determining "substantial compliance" as a checklist, but rather as suggestions. The first and last recommendations are the most substantial; the HSRB likely will always consider the nature and number of deficiencies and the likely significance of the deficiency for research subjects. The other recommendations might have relevance occasionally and might consciously or unconsciously influence decisions about the seriousness of a violation. Overall, the Board should not be rigid on these matters. The final conclusion should make no reference to intent, only whether the protocol achieves substantial compliance or not, the definition of which likely will evolve over time. Dr. Fisher agreed in principle with Dr. Brimijoin, but stated that she would not adopt these recommendations as HSRB guidelines if "intent" was included. She agreed that decisions on compliance would focus mainly on the nature and number of deficiencies and the likely significance of the deficiency for subjects of the research.

Dr. Fisher disagreed that the Board does not judge whether a protocol is unethical after it has been conducted. If the HSRB finds evidence of harm, they must find that the protocol was not in substantial compliance; the final decision for using the data rests with EPA. If the data will offer improved protection for the public, it must be acknowledged that the study may have been unethical, but the benefits outweigh this. Dr. Sharp stated that he was not suggesting that the HSRB cannot pass judgment if a past study was unethical; however, the Board cannot protect these subjects from harm but can only perhaps protect their dignity from harm by recommending against EPA use of the data. Dr. Fenske agreed, adding that if the study involves third party research, such as use of a contractor who may not follow protocols diligently, the HSRB's judgment of the study and disapproval may protect future subjects by bringing scrutiny to the contractor. Dr. Fisher agreed, adding that issues of justice apply–recognition of unethical behavior is justice. The regulations state that EPA will not use the data if the data were obtained in an unethical manner. Dr. Menikoff suggested that evaluating "intent" may allow the Board to reject data from a study that did not have egregious violations, but failure to reject the data could mean that this violation is not taken seriously by future investigators, which could lead to harm to future subjects.

Dr. Fisher concluded that EPA recommendations concerning the nature and number of deficiencies and the likely significance of the deficiency for research subjects could be formally addressed by the Board. Other recommendations may arise during Board deliberations and can be considered, but will not be formally adopted as guidelines.

Dr. Fisher returned discussion to WPC-001, regarding determination of a pathogen-free region surrounding the test site. Dr. Carroll must ensure that the region is pathogen-free, or must trap mosquitoes during the study for testing for pathogens. Mr. Carley stated that the Board must consider whether using sentinel flocks is the best indicator of a pathogen-free region or if testing pools of mosquitoes is more indicative of a pathogen-free region. It is also critical to determine the size of the "pathogen-free region." Dr. Lebowitz stated that it is critical to determine that the mosquitoes collected during testing are pathogen-free. If this is not the case, a subject may have been infected, which is a critical ethical issue. The current standard is to use pools of trapped mosquitoes. Entomologists and infectious disease experts likely have information concerning the region need to consider an area to be free of potential risk, and also on the behavior of

mosquitoes that informs determination of the risk area. Sentinel flocks are a secondary measure of a pathogen-free area, but this information can be obtained more quickly than mosquito testing. Dr. Philpott commented that the best approach may be to rely on experts in this area, as Dr. Carroll did. Procedures should be redefined to reflect that if experts conclude that disease is absent from an area, this is acceptable. Dr. Carley asked whether inclusion of a letter from the local mosquito control agency would suffice. Dr. Fisher agreed that this was permissible, or the investigator could include the agency's monthly report concerning the presence of pathogens. She also suggested that if there was concern because of detection of a pathogen in a sentinel flock, serological testing of mosquitoes caught during the study could be performed; a plan for alerting subjects if a pathogen is found during mosquito testing should be developed.

Follow-up From Previous Day's Discussion

Mr. Jordan had no follow-up comments from Wednesday's discussions. Mr. Carley verified that a product containing 40 percent OLE in a pump spray formulation is registered with EPA. He also reported that 100 percent of all human studies reviewed by the HSRB to date have been subject to EPA audit. All research records have been found to be complete and there were no GLP issues.

Dr. Fisher introduced two consultants who participated in Board deliberations at this meeting. Dr. Yiliang Zhu is a professor and directs the Biostatistics Ph.D. program and the Center for Collaborative Research at the Department of Epidemiology and Biostatistics, College of Public Health, University of South Florida. He has served on several advisory committees, including the NAS/National Research Council committee on EPA's reassessment of dioxin risks and serves on the Organ Transplant Advisory Committee at DHHS. His research focuses on quantitative methodologies in health risk assessment. Dr. David Hoel is Distinguished University Professor in the Department of Biostatistics, Bioinformatics, and Epidemiology at The Medical University of South Carolina, Charleston, South Carolina. Dr. Hoel worked at the National Institute of Environmental Health Sciences as Director of the Division of Environmental Risk Assessment. He has served on a number of advisory boards and has an interest in the modification of adverse health effects caused by environmental factors such as chemicals and radiation.

HSRB Workgroup and EPA Process on Confidential Business Information (CBI) Redacted Submissions

Mr. Jordan described two skin irritation studies which involved the first claims of CBI for a study reviewed by the HSRB. These studies differ from those quantifying effect levels for hexavalent chromium because they seek to categorize products within a range of irritators or sensitizers. Neither product is expected to cause irritation or sensitivity; nonetheless, the studies excluded from the study population those who might be sensitive to the products. The hexavalent chromium studies also employed a repeat open application testing procedure, whereas these studies were conducted by application of the product via patches placed in direct contact with the skin.

The products involved in these studies also were subject to CBI claims. The Board had previously proposed a process for handling CBI issues, with the goal of providing as much information to the HSRB as possible, ensuring adequate information for a sound review, and permitting the review to be conducted during a public meeting. The Board did not receive information deemed CBI by the sponsor. The CBI process also seeks to encourage sponsors to make CBI claims only when necessary and to limit their scope, providing for an informal EPA assessment of the appropriateness of CBI claims. If EPA finds the claims to be reasonable, EPA will provide redacted material to the HSRB Chair. The Chair will appoint members of the HSRB to a workgroup to review the redacted material and inform EPA whether the material provided is adequate for a sound review. If concerns are raised by work group members, EPA and the Chair will discuss whether the Board can have access to additional non-CBI information that addresses the workgroup's concerns.

For the protocols discussed at this meeting, initial CBI claims were broad, but after discussion, the sponsor agreed to limit the CBI claim. The Board workgroup reviewed the materials and determined a need for further information, which OPP has attempted to provide. The most important information requested by the work group was toxicity data; a summary of toxicity information on three major active ingredients in insect repellents was provided, but the ingredient(s) used in the studies themselves was not identified.

Dr. Fisher provided further detail on how the process for working with CBI claims was developed. An overarching issue was the need for Board deliberations to remain transparent to the public, and respect both the CBI claims of the sponsor, and the responsibility of EPA to respect and protect CBI. In cases for which EPA believes CBI claims are invalid, the Board wishes to support EPA.

As part of the process, EPA contacts registrants who may make a CBI claim to inform them that materials and information not claimed as CBI will be reviewed by the HSRB in a public session. EPA encourages the registrant to provide as much information to the Board as possible, to facilitate accurate assessment of the scientific validity and value of the study, the safety risks to subjects, and the human subjects' protection. The Board anticipates that toxicity data on an ingredient whose identity is claimed as CBI and other forms of safety and efficacy information will frequently be necessary for Board review. One example of potential CBI is the name of the sponsor, which could be redacted from the Investigational Review Board (IRB) report and ICFs. Additionally, EPA can provide the Board with a statement that EPA has identified no unethical conflicts of interest between the sponsor, investigator, and potential subjects. The DFO can determine whether there is a statutory conflict between Board members' HSRB responsibilities regarding the protocol and private interests and activities. If the active ingredient is claimed as CBI, the registrant can provide animal or human toxicity data that will assist the Board with safety and efficacy evaluations.

After completion of the prior tasks and gathering of redacted materials, EPA holds an planning meeting with the Board Chair and DFO to discuss the nature of the CBI claim, information the Board will not be able to view because of the claim, and steps that will be taken to provide the Board with sufficient information for its review. After the planning meeting, the Chair will identify Board science and ethics members who would be most appropriate to serve as

primary reviewers of the protocol. These HSRB members will receive the question(s) EPA will ask the Board to address; a general description of the nature of the CBI and non-CBI materials; and a description of supporting information regarding the CBI claims that will be made available to the Board. Drs. Fisher and Fenske were chosen to serve as workgroup members for the protocols with CBI claims discussed at this meeting.

The workgroup analyzes the available information and reports to Dr. Fisher whether the information would be sufficient to help the Board answer EPA's questions and if not, what additional non-CBI materials or statements by EPA regarding the nature of the CBI information would be required. The Chair will review the workgroup's analysis and communicate to the HSRB DFO the Chair's evaluation of whether additional information is needed for Board review. The Chair will request that EPA, to the extent legally permissible, provide the information to the Board.

A description of the general nature of CBI and steps taken to provide background information within legal limits will be included in the materials submitted to the full Board for review. A representative of the registrant may make a presentation and answer questions at the public meeting to ensure the Board has adequate information to advise EPA and to ensure that CBI is protected at the open meeting.

The workgroup evaluation of the materials for the patch test studies discussed during the meeting found an absence of toxicity data; no rationale for the dose level selected; no information concerning whether the experimental dose level is the level that consumers would use; an informed consent document that indicates five insect repellents but study reports for only two; and a lack of background information to assess the risks to participants. During the planning meeting, EPA stated that this information could be obtained based on publicly available information. Dr. Fisher expressed surprise that most of this information was not initially provided, and that EPA did not know it was not provided. A letter from EPA indicating what additional information they can provide would be useful.

Completed Skin Patch Tests

Background

Mr. Carley presented background information on the completed skin patch tests conducted with two insect repellent products. The products tested in this and the repeat insult patch test (RIPT) study are intended to be applied repeatedly to large areas of skin and thus should be non-irritating. The sponsor has performed these tests to confirm non-irritation and characterize any irritation or sensitization potential.

The first submission of documentation occurred in May 2006. While these are pre-rule studies, 40 CFR §26.1303 still applies because further documentation was submitted in November 2006. The November 2006 submission contained broad claims of confidentiality. In February 2007, the sponsor resubmitted the study with narrowed claims of confidentiality, in both complete and releasable redacted versions. Responses to EPA reviewer questions were submitted in March 2007, in both complete and releasable redacted versions. These studies

involved third-party research with intentional exposure of human subjects, intended for submission to EPA under the pesticide laws. Because the studies were initiated before April 7, 2007, pre-review of the protocol was not required and applicable ethical standards are 40 CFR §26.1703 and §26.1704.

The studies were submitted with supplemental claims of CBI. FIFRA §10(d)(1) requires EPA to protect from disclosure the identity or concentration of pesticide inert ingredients in pesticide products, and information concerning manufacturing or quality control processes for a pesticide product. The scope of supplemental claims can include the identity of the sponsoring company, product name and form, or the identity and concentration of the active ingredient. Claims of confidentiality must be substantiated. In this case, the registrant argued that making public the applicant's name, trade name of the proposed product and form, and composition of the new product prior to registration approval would place the registrant at a competitive disadvantage.

These studies underwent the pilot process on CBI redacted submissions as described. Concerns of the HSRB workgroup included a lack of information concerning the identity and concentration of active and inert ingredients in the tested products. To address this concern, EPA has received complete information on product composition in the Confidential Statements of Formula submitted by the registrant and has informed the HSRB that the active ingredient currently is registered as a repellent by EPA and occurs in these products at concentration ranges previously approved for other products containing this ingredient. The HSRB workgroup also expressed concern about the lack of toxicity information provided for the product ingredients. EPA received other toxicity information on the formulated products, including toxicity profiles of the component ingredients, published reports of irritation and sensitization potential, and provided World Health Organization (WHO) profiles of registered repellent active ingredients to the HSRB. The HSRB workgroup also noted a lack of rationale for dose levels. EPA informed the work group that the dose used (0.2 ml of product on a 2 cm-by-2 cm patch) is standard practice in cosmetics and consumer products patch testing. Additionally, the patch dose of 0.2 ml/4 cm2 is equivalent to 30 ml/600 cm2, which is approximately 30 times the typical user repellent application rate; this elevated dose is appropriate for these patch tests. The work group's final concern focused on the lack of information reported for other materials included in the studies. These studies represent multi-material, multi-sponsor patch studies, with single-material reports, which is common practice in cosmetics and consumer products testing. The patches are separated during testing, and thus no interference between test materials is expected.

Dr. Fisher questioned why FIFRA considers manufacturing or quality control processes CBI. Mr. Carley explained that the purpose behind this provision was to protect pesticide registrants from being forced to disclose information that would offer competitors an unfair competitive advantage. Dr. Fisher asked whether quality control processes could impact the safety or quality of the ingredients. Mr. Carley indicated that this was not a concern. He explained that the scope of these protections actually is narrow. The U.S. Supreme Court concluded that the phrase "health and safety data" is broad, but information concerning manufacturing and quality control processes must be made public 30 days after registration, and that certain ingredients must be listed on labels.

Dr. Fenske commented on the lack of rationale for dose. If the rationale for a given dose is "standard practice," documentation should be included. For example, if the procedure is Food and Drug Administration (FDA) approved, some statement to indicate that it is approved by a government agency for cosmetic and consumer products would be helpful. Mr. Carley agreed, adding that EPA does not have guidelines for accepted protocols for these studies. Submitters have attached articles from the Cosmetic, Toiletry and Fragrance Association describing a range of practices, but the articles do not describe the best way to perform such testing. The most accurate way to consider this is to understand there are different ways to perform these studies that fall into several general categories; if done often enough by a given laboratory, the protocols become routine, although they do not really become standardized. Dr. Roger Gardner (OPP, EPA) added that for pesticide tests on animals, there are standard procedures with recommended doses based on a large database of information. The goal of the studies is to determine if irritation can be induced; the criterion calls for choosing a dose at which irritation is likely to occur. Dose also is only qualitatively related to anticipated consumer exposure; most guidelines call for exceeding this dosage. Dr. Fenske reiterated that because there do not appear to be recommendations for human studies available through EPA, information from other agencies, such as FDA, would be helpful. Dr. Gardner explained that late in the review process for these studies, EPA found that FDA has draft guidelines; however, insufficient time was available to ascertain the rationale for dosing.

Dr. Fish inquired whether the dose range was consistent with those used in Dr. Carroll's studies. Mr. Carley responded that these are very limited dose studies and are not appropriate for extrapolating dose to the very different materials tested in the primary irritation studies. For repellent testing, a dose of 1 g/600 or 650 cm^2 is used, based on a survey of DEET users, to approximate consumer dose of a repellent.

Dr. Menikoff noted that five compounds had been applied to subjects, but the results of only two of these are reported. He asked if EPA knew the identity of the other three compounds. Mr. Carley indicated that EPA does not know the identity of the compounds; registrants indicated that these were "developmental compounds." Dr. Menikoff remarked that this had implications for informed consent and asked if it had been verified that subjects received truthful information about the compounds. Mr. Carley explained that these questions would be addressed during EPA's review of the studies. He added that five materials were used in the 48-hour irritation study, but 16 were used in the RIPT study; most of these materials were provided by other sponsors and EPA does not have information on their identities. Dr. Kim inquired how EPA could rule out interference among materials if the identity of the other materials is unknown. Dr. Gardner responded that dermal effects are specific and local. The selection criterion of dosing for sensitization is different from that of dose selection for irritation. There also are dermatologic indicators that differentiate between irritation and immune responses indicating sensitization. The effects of irritation studies are local, similar to the effects of food allergy skin tests.

Dr. Lebowitz questioned if EPA asks toxicologists to verify information from registrants concerning the toxicity of ingredients found in the products. Mr. Carley confirmed that this was the case. Dr. Lebowitz also asked whether animal toxicity skin testing literature was used to determine if products had potential sensitization capabilities before testing the products in

humans. Dr. Gardner explained that animal test results (using guinea pigs) are available for sensitization potential of active ingredients in pesticide products. This information is required. EPA relies on background data as well as toxicity tables to assess sensitization potential. Dr. Fisher noted that these tests use the assumption that each patch has independent effects. She cautioned that there are practices over which EPA has no control, such as the participation of multiple sponsors and use of multiple materials in a single study. The Board must be alert to potential problems arising from this situation.

48-hour Primary Dermal Irritation Study

Background

Mr. Carley presented background information on the 48-hour Primary Dermal Irritation Study. Documents were submitted covering product A (MRID 47077101, Code 1000718-008) and product B (MRID 47093901, Code 1004006-005). Supplements, both identical in content, were also submitted for each product (MRIDs 47077201, 47077601 for products A and B, respectively). Products A and B are both repellents containing the same EPA-registered active ingredient at concentrations within a previously accepted range, and contain similar pesticide inert ingredients.

Each of the two study reports describes results for one of five substances tested in a single execution of the protocol with a single subject panel; results have been submitted for two of the five substances tested. All subjects were non-pregnant, non-nursing consenting adults, free of skin disease, not sensitive to similar products, and not using medications. The study enrolled 54 subjects; 53 completed the study.

The study schedule called for application of 0.2 ml of five test materials to 2 cm-by-2 cm Webril patches (five patches per subject), followed by air-drying for 30 minutes before application of the patches to each subject's back. Forty-eight hours after application, the patches are removed and sites evaluated. If the first evaluation is positive, a second reader re-evaluates the site. Seventy-two hours after application, the sites are evaluated again.

The dermal LD50 limit dose is greater than 2,000 mg/kg for the active ingredient. The margin of exposure (MOE) for an applied dose of 0.2 ml to a 70 kg adult is greater than 350. Skin loading of 0.2 ml/4 cm2 is approximately 30 times loading at the "typical consumer dose" of a repellent (1 g/600 cm2).

Science Assessment

Dr. Gardner presented EPA's science assessment of the 48-hour Primary Dermal Irritation Study. EPA requires primary dermal irritation data under 40 CFR Part 158 for registration of all products. Guidance for conducting animal tests of irritation is published under EPA's Office of Prevention, Pesticides and Toxic Substances Test Guideline 870.2500 and corresponds to Organisation for Economic Cooperation and Development Test Guideline 404. The results from such studies are used to identify possible effects from exposure of the skin to the test substance and are used to support precautionary labeling.

EPA classifies irritants according to toxicity category. Category I substances are corrosive and/or scarring; Category II substances can cause severe irritation at 72 hours (severe erythema or edema); Category III substances can cause moderate irritation at 72 hours (moderate erythema); and Category IV substances cause only mild or slight irritation (no irritation or slight erythema). Standard precautionary statements are based on the toxicity category. For example, the label for a Toxicity Category III substance might include language cautioning consumers to avoid contact with skin or clothing and to wash thoroughly with soap and water after handling. Toxicity Category IV substances do not require precautionary statements, but registrants may choose to use Category III labeling standards.

EPA encourages minimization of unnecessary animal testing. EPA does not encourage human irritancy testing, but has accepted it in place of animal testing in some cases. The submitter of this study requested a waiver of the usual requirements for animal testing of dermal irritation, because each component in the products tested is discussed in published literature, has a history of use as an intentional food additive or in cosmetics products directly applied to human skin, and is well-known to EPA. The waiver request also argues that there is published literature on product components that indicates most are mild to slight irritants that would be classified as Toxicity Category IV. A few of the substances are moderate irritants that would be classified in Toxicity Category III, with labeling to "avoid contact with skin."

Subject inclusion criteria called for males or females who were at least 18 years old and in general good health; were free of any systemic or dermatologic disorder which would interfere with the results of the study or increase the risk of adverse events; were of any skin type or race, given that the skin pigmentation allowed discernment of erythema; had completed a medical screening procedure; and had signed an ICF. Exclusion criteria excluded subjects who had any visible skin disease which would interfere with the evaluation; were receiving systemic or topical medication which would interfere with the study results; had psoriasis or active atopic dermatitis or eczema; were pregnant, planned to become pregnant during the study, or were breast-feeding; and/or had a known sensitivity to cosmetics, skin care products, insect repellents, or to topical drugs related to the material being evaluated.

The study enrolled 54 participants; one participant withdrew. The participants included 48 females and six males, ranging in age from 19 to 71 years (average age was 51 years). Subjects were primarily Caucasian.

The study protocol involved application of 0.2 ml of five test materials to 2-by-2 cm Webril patches (five patches per subject), followed by air-drying for 30 minutes before application of the patches to each subject's back. Forty-eight hours after application, the patches are removed and sites evaluated. If the first evaluation is positive, a second reader re-evaluates the site. Seventy-two hours after application, the sites are evaluated again.

Reactions were graded using a +/- system. The reaction categories were no reaction (-); minimal or doubtful response, slightly different from surrounding skin (?); definite erythema, no edema (+); definite erythema, definite edema (++); and definite erythema, definite edema, vesiculation (+++). The Primary Irritation Index (PII), used for classification, was calculated as

the higher mean score at either the 48-hour or 72-hour observation, calculated by dividing the sum of reaction scores for all subjects at each observation time by the number of subjects in the group. A PII of 0.50 or less indicates that the product is essentially non-irritating; these products are the equivalent of Toxicity Category IV.

Results and Discussion

Most of the responses in this study were in the marginal category. A "?" was used when response effects were reversible, and thus indicate irritation, not sensitization. A high proportion of subjects had marginal responses, which could be a result of having an occlusive patch on the skin. Two areas of concern include a lack of untreated patches as negative controls, rendering questionable the association of observed responses with the test substance. Additionally, the patches were dried before application, which resulted in a markedly different pattern of exposure from typical use of a topically applied repellent. The rationale for this approach was to ensure that the liquid product remained at the test site so that a dose exceeding the typical consumer dose was achieved. Dr. Gardner expressed concern that this approach resulted in a lack of skin contact by volatile components of the products, which would evaporate before patch application. Changes in the products' physical characteristics as they dry could affect the irritation potential of the products.

The lack of negative controls and different pattern of exposure represent significant scientific limitations; however, the data are considered sufficiently reliable to be used in conjunction with other information on the irritancy potential of product ingredients to support the conclusion that these formulations do not cause more than mild skin irritation.

Ethics Assessment

Mr. Carley presented EPA's ethics review of the 48-hour Primary Dermal Irritation Study. He noted that the Board had expressed concern that if the identity of the sponsor was subject to CBI, conflict of interest issues could arise; he informed the Board that EPA had not identified any conflicts of interest.

Applicable ethical standards include 40 CFR §26.1303 (defines standard for documenting ethical conduct of research), 40 CFR §26.1703 (forbids EPA reliance on research involving intentional exposure of pregnant or nursing women or children), and 40 CFR §26.1704 (forbids EPA reliance on research if there is "clear and convincing evidence" that its conduct was fundamentally unethical or significantly deficient relative to standards prevailing when it was conducted). The initial submissions did not address the requirement of 40 CFR §26.1303 to document ethical conduct. Resubmissions are adequate to support review; however, discussions of risk, risk minimization, benefits, and risk/benefit are weak, but acceptable for pre-rule studies.

The purpose of this study was to determine the ability of two experimental repellent products (and three other unidentified materials) to cause immediate irritation by application to human skin under controlled patch conditions. The sponsor's policy is to avoid "unnecessary use of animals in testing;" thus, this study was submitted to support a request for waiving EPA's normal requirement for animal testing of irritancy.

The 54 subjects enrolled in the study (53 completed it) were selected from among subjects who previously participated in research at this laboratory; they were recruited as they completed a previous study. The subjects received $30 compensation for three visits, which was considered likely to attract primarily economically disadvantaged subjects. There were no other indications that subjects were from vulnerable groups. The risks associated with participation were described to subjects in generic terms; both the irritation and RIPT studies were described identically. Although identifying weak irritants before marketing and use has potential societal benefit, this assay is unable to identify weak irritants. EPA concluded that, if scientifically acceptable, the benefit of this study probably justifies the low incremental risks to subjects.

The study was reviewed by the Allendale IRB (AIRB) of Allendale, Pennsylvania, which is registered with OHRP but not known to be accredited. The submitted documentation of IRB composition, procedures, and review meets regulatory requirements. General compliance with FDA rules was asserted by TKL Research, which performed the study.

Written consent was obtained from all subjects, using an ICF approved by the AIRB. This document was highly generic and sometimes unclear, and the consent process emphasized reliance on frequent test subjects, and on establishing their eligibility rather than their fully informed understanding. Review of applicable documentation found that subject privacy was not compromised in the reports. The subjects were paid only upon completion of the study, which may have unduly influenced subjects not to withdraw. Subjects also were offered a "finder's fee" for referring others, but were paid only if the referral completed testing, which also may have unduly influenced referral subjects not to withdraw.

Ethical concerns include recruitment of subjects from a population of frequent test subjects, without explicit consideration of representativeness. The compensation was low and may have disproportionately attracted economically disadvantaged subjects. Compensation was tied to completion of the study, which may have compromised freedom to withdraw. Additionally, although possible lasting effects (change in skin pigmentation, generation of allergies) were acknowledged, treatment promised only "to relieve the immediate problem," and only for undefined "significant reactions." A troubling qualified promise was made to identify the agent that induced an allergic reaction. There was unnecessary identification of subjects by Social Security Number. Because the assay may be inadequate for identifying weak irritants, this study may be inappropriate for determining irritation category.

There were some gaps in documentation of ethical conduct, but documentation was relatively complete for pre-rule research. There was no clear and convincing evidence that the research was fundamentally unethical and no intentional exposure of children or pregnant or nursing women occurred. EPA had many ethical concerns about this study, but concluded that the research was consistent with common practice in testing cosmetics and other consumer products not regulated as pesticides. There was no clear and convincing evidence that the research was significantly deficient relative to prevailing standards.

The charge to the HSRB was to determine whether these studies are sufficiently sound, from a scientific perspective, to be used as part of a weight-of-evidence assessment to evaluate

the potential of the formulations tested to irritate human skin and to determine if there is clear and convincing evidence that the conduct of these studies was fundamentally unethical, or significantly deficient relative to the ethical standards prevailing at the time the research was performed.

Mr. Jordan corrected the MOE for subjects in this trial as being greater than 60,000 to 70,000, not 350 as previously reported.

Dr. Fisher inquired if the data, if used, would increase consumer protection. Mr. Carley explained that the basic requirement for consumer protection is an animal study. This protocol was submitted to request EPA waive animal tests. Thus, EPA cannot determine if testing in humans would provide information significantly different from that derived from animal testing.

Dr. Fish inquired whether readers of the dermal reaction were blinded. Dr. Gardner responded that no information was provided on blinding. Because control patches were not used, blinding would only mask the identity of the different products.

Dr. Menikoff asked about the relationship between human and animal testing, particularly whether a company could seek EPA approval for a product based only on animal testing. Mr. Carley explained that the standard data requirement for these products is a standard animal test of dermal irritation. Dr. Gardner added that in the waiver rationale, the registrant argues that because the products would be applied directly to the skin, the results would confirm a body of evidence on separate components that suggest no irritation. With potentially dangerous products, EPA labels reflect the most dangerous component, regardless of product composition. For these products, a person who experiences irritation likely will discontinue use; further consideration of consumer behaviors falls under risk management.

Dr. Brimijoin asked Mr. Carley to expand on concerns that the assay is of dubious value because it does not identify minor irritants. Mr. Carley explained that the study report indicates the evaluation method used will screen out strong irritants, but not weaker irritants that require multiple exposures. Dr. Brimijoin inquired if this affected the Board's response to the first charge question, concerning whether the studies were sufficiently sound to evaluate the potential of the products to irritate human skin. He asked whether knowledge that the registrants have excluded the possibility of major irritation could be considered a major part of a weight-of-evidence assessment. Dr. Fisher questioned whether the purpose of the study was to identify all levels of irritation or only severe levels; the registrants admit they cannot evaluate low levels of irritation. She requested clarification on the value of the study claimed by registrants and the value of the study to EPA. Mr. Jordan explained that EPA has a large amount of information about this formulation and its ingredient. EPA requested the Board's opinion concerning the scientific soundness of the study, and to describe its strengths and limitations. EPA seeks to assign this formulation to one of four irritant categories. The product is likely to fall into Category IV (non-irritant) or Category III (slightly or mildly irritating). EPA will make labeling decisions based on the assigned category.

Dr. Philpott raised the issue of the registrant's request for a waiver for animal testing, and whether EPA believes there is sufficient evidence from animal and in vitro testing to support this

request. Dr. Gardner explained that data were provided as published literature. EPA has significant experience with these types of pesticide studies, and it is not difficult to make extrapolations based on data from individual components. EPA takes a conservative approach to identifying risk; labeling is based on the highest toxicity category of an ingredient in a product.

Dr. Lois Lehman-McKeeman asked Dr. Gardner if EPA had confirmation of product composition and whether, under standard clinical practices, analytical verification of composition is required. Dr. Gardner responded that analytical verification was not required because the products in the study are of known composition; product composition information was supplied and certified by the registrants. They provided a confidential statement of the formula that reports a range of ingredients and product chemistry characteristics, such as stability.

Dr. Krishnan inquired whether, given that five products were tested simultaneously, there was concern that the actual MOE is lower than that calculated. Dr. Gardner stated that this was not a concern because the products are already known to be of low toxicity. If there is a direct, acute effect; this effect will not extend to the other products unless the other products are sensitizers, which this assay cannot determine. The MOE for all the products likely is low, and aggregation of MOEs would result in a low MOE.

Public Comments

Dr. James Milbauer and Ms. Milena Reckseit of TKL Research

Dr. James Milbauer (TKL Research consultant) explained that TKL Research performed the patch testing for a corporate sponsor seeking weight-of-evidence to address the issue of a waiver for animal testing. The patch test protocol used is based on a long record of literature published since the 1950s by academic dermatologists and others. Despite this record, specific protocols for performing patch testing are not available, although most investigators perform the testing similarly. The patch test commonly is used for diagnosis of contact dermatitis.

The manufacturer performed preclinical testing before beginning human testing to determine the safety of the product. The sponsor believes that, because different species react differently to substances, human patch testing, although not required by EPA, would further ensure the safety of those using the products.

Dr. Milbauer addressed the inability of this test to measure weak irritants. He commented that most irritants are distributed along a gradient of irritation potential, and pre-clinical testing screens out the greatest risk associated with the product. This test widens the sponsor's "comfort level" concerning this product. The sponsor realizes that the weakest irritants that require repeat exposure to induce irritation will not be identified in this test. Additionally, no test can ensure that no one in a population will react to a product, but testing can determine that the product will be safe for most users.

Ms. Milena Reckseit (TKL Research) addressed the Board's questions concerning the attractiveness of the low amount of compensation ($30) to primarily financially disadvantaged

people. She explained that most subjects lived in New Jersey or in one of four New York metropolitan areas and hale from a range of socioeconomic and demographic populations. The majority of the subjects (71.5 percent) are from towns with average household incomes greater than $66,000, in contrast to the average American household income of approximately $42,000. On average, 60 percent of inhabitants of the areas from which subjects came are in the labor force, and slightly more than 60 percent own their own home; approximately 4.3 percent of the population live below the poverty level. Approximately 93 percent of study participants were white, were largely female, and most ranged in age from 35 to 64 years. Roughly 71 percent of study participants live in towns approximately 3 miles from the site; the subject fee of $30 ($10 per visit) was considered reasonable in part because participation required little travel.

Dr. Fisher asked Dr. Milbauer and Ms. Reckseit to clarify the AIRB's response to the lack of information on three of the five materials tested in the 48-hour Primary Dermal Irritation Study. Dr. Milbauer explained that the AIRB received verbal communication from the sponsors that the other three products are approved and marketed repellents. The sponsor wanted to ensure that the new products were no more or less irritating than the other three products. Dr. Fisher inquired whether the AIRB received a risk-benefit analysis for all five products and how the AIRB could determine the ICFs are appropriate across all five products. Dr. Milbauer responded that he was not involved in the informed consent process, but believed that the AIRB received information for all five products.

Dr. Fish asked Dr. Milbauer to explain the practice of using a second reader to assess irritation and why the study was not blinded. Dr. Milbauer explained that it is not standard to use blinding in these types of studies. An objective reaction—is the skin red or not, or is the reaction questionable—was being assessed. A second reading was performed after 15 minutes; the report indicated that if a reading was positive, a second reading was performed by a different reader. Dr. Milbauer could not confirm whether the same person had performed all readings.

Dr. Chadwick asked whether the sponsor or TKL Research, or another body, developed the protocols. Dr. Milbauer answered that a Board-certified dermatologist (Dr. Jonathan Dosik) was listed as the investigator on the protocol. TKL Research does write protocols for clients, but Dr. Milbauer could not confirm whether this was the case for this study.

Dr. Philpott inquired whether the AIRB read and approved the telephone script for recruitment. Ms. Reckseit explained that no advertising or telephone screening was performed for the Primary Dermal Irritation Study. The subjects participating in this study had participated in a previous TKL Research dermal safety study. TKL Research has processes in place to determine that subjects were eligible to participate in the Primary Dermal Irritation Study. TKL Research maintains a large database of subjects who participate in dermal safety studies. The processes are routine, because TKL Research has data indicating that these subjects are "patch qualified." At the recruitment level, the subjects are considered "prospective subjects" during the in-person interview and undergo onsite medical screening and a formal consent process before enrollment in the study. Dr. Philpott noted that because a telephone interview would collect personal health information, verbal informed consent should have been obtained from participants, despite their being considered "prospective subjects." Ms. Reckseit explained that for the Primary Dermal Irritation Study, experienced recruiters privately interviewed each

subject and informed them about this new study. The subjects were already known to be "patch qualified." TKL Research has the subject information, and upon enrollment in the new study, their information was re-entered into the database and labeled with a start date of April 26. Based on this date, eligibility reports were issued indicating the subject's correct age, patch-qualification, current residence, and any dermatologic conditions indicated in their medical history. The reports are issued to clinic staff; the informed consent process begins at the in-person medical screen. The ICF is signed after completion of the medical screen.

Dr. Fenske questioned whether allowing the test materials to evaporate on the patch for 30 minutes would affect the irritation potential of the materials. Dr. Milbauer explained that this is standard procedure in clinical and industry practice. Volatile compounds evaporate rapidly during use of a product and thus will not be persistent against the skin. Trapping these compounds against the skin with an occlusive patch creates an artificial, potentially irritating situation that could obscure the irritation potential of the product itself. Dr. Fenske requested clarification of the fifth exclusion criterion that excludes anyone with known sensitivity to products related to the material being evaluated and how many people this was expected to encompass. Dr. Milbauer stated that he would expect a small number of people to be affected by this; subjects are asked if they are allergic to repellents or cosmetics and are excluded if they are. The rationale for this exclusion criterion is to avoid testing people with a history of allergies. Allergies probably are irrelevant to the testing of these products, but the sponsor believed it was safer to exclude people with known allergies. Dr. Fenske inquired whether Dr. Milbauer would expect the product to be labeled in such a way that would caution this population against using it. Dr. Milbauer responded that they try not to provoke allergic reactions when testing irritation. Allergies do not, however, predispose people to irritation.

Dr. Fish asked whether Social Security Numbers were collected for payment purposes and if they were kept separate from research data. Ms. Reckseit explained that both these conditions were true. Dr. Fish noted that the study documentation includes Health Insurance Portability and Accountability Act (HIPAA) language, but most contract laboratories are not covered by HIPAA. Ms. Reckseit added that TKL Research wants to be conservative and assure subjects their health information will not be used beyond the scope of the study, and therefore works to be HIPAA-compliant.

Dr. Suzanne Fitzpatrick inquired if investigators ensured that test patches were not applied to the same spot on the back as patches tested by repeat subjects in previous studies. Ms. Reckseit explained that the test area is delineated by a line on the subject's back, and that area is not used in a subsequent study. As part of enrolling in a second study, clinical staff determine that subjects have no residual irritation or other problems on the skin on their backs.

Mr. William McCormick of The Clorox Company

Mr. William McCormick identified himself as a Board-certified toxicologist working for The Clorox Company. He performs toxicity testing related to EPA registration of products. He clarified the endpoint—primary skin irritation—addressed in the study under discussion. The primary irritation index in humans measures acute irritation, thus, non-identification of weak irritants is accurate. A second study of irritation in humans is the cumulative irritancy study,

which involves 21 days of application to identify weak irritants. The Primary Dermal Irritation Study tests for the primary irritation endpoint and thus is a grosser estimate of irritation. He added in response to Dr. Fisher that companies often tend to prefer using humans for these studies, rather than animals, such as rabbits. Dr. Fenske asked whether the primary skin irritation test would be sufficient to determine if the products are Category III or Category IV irritants. Mr. McCormick answered that this test would permit such categorization.

Board Discussion

Dr. Hoel expressed surprise that EPA and HSRB are discussing what appears to him to be more suitable for FDA consideration, considering the human health effects associated with the products. Because FDA regulates cosmetics, the approaches used in this regulation could be applied to these studies. He commented on the lack of eye test data for these products, which is a primary concern, particularly if a product is applied using a sprayed-on formulation. Possible inhalation also could be a concern. He questioned why, if the active ingredients and vehicle used in the products are approved, the products themselves were not, unless there was concern over interaction of the ingredients. Dr. Hoel also questioned why, given that three animals are usually considered sufficient for an animal test, a company would decide to test its products on 50 humans.

Dr. Hoel commented that the $30 compensation payment to research subjects could be considered almost a volunteer-level of compensation. He added that the subject population selected did not appear to be representative of the population as a whole.

Concerning analysis of outcomes, Dr. Hoel noted that three of the 50 subjects had adverse events, the rest had minor or no outcomes, but the average score was the same. Ordering could be used to strengthen the statistical analysis; however, problems include determining who a group would be compared to, how power is determined, and lack of negative controls.

Scientific Considerations—48-hour Primary Dermal Irritation Study

Dr. Fenske opened the HSRB scientific review of the study. He stated that EPA's decision to label the product as Category III prompted the sponsor to perform the study. EPA raised concerns related to applying the product to a patch and allowing it to dry before application. Dr. Milbauer explained the rationale for this approach. In Dr. Fenske's opinion, the application procedure is valid because use of an occlusive patch could permit moisture to develop and allow product and/or solvents to penetrate into the skin and cause irritation. The occlusive nature of the patch itself would be a confounder for irritation.

Of those cases marked as positive for irritation (7), the irritation had resolved to questionable status by 72 hours after application of the patch, indicating reversal of irritation. Testing for 72 hours is considered acceptable. Negative controls are not routinely used for testing of this sort, which is a difference between academic and third-party research. Dr. Fenske speculated that an unfavorable finding could be a serious consequence for third-party researchers; although well-trained and scrupulous, there is the potential for bias if third-party researchers seek subsequent contracts from a sponsor. A negative control and blinding would

have strengthened the study, but this is not a fatal flaw. Inclusion of these conditions would help determine whether the questionable findings were caused by the product or the patch itself.

In its data evaluation, EPA states that the studies were incomplete and could not be used for regulatory purposes, but in its presentation EPA stated that the studies could be used for determining the irritancy potential of the ingredients. Dr. Fenske agreed with Dr. Hoel that it would be important to determine the number of people in each of the reaction categories; however, the study identifies the numbers. Additionally, no subjects had high irritancy scores by 72 hours after patch application. Dr. Fenske concluded that irritation noted at 48 hours had reversed at 72 hours, which suggests that application of the products resulted in minimal response in the test population.

Dr. Lehman-McKeeman concurred with Dr. Fenske's assessment. Her overall sense of the data was that the study was designed to assess dermal hazard and there was no indication of this in any of the subjects. There are some limitations to the study, but no flaws that preclude use of the data. She stated that she was personally scientifically unconvinced that performing this study in humans was necessary, because rabbit studies would have adequately addressed the issue of dermal irritation. Dr. Fisher reminded Board members that the HSRB also was asked to consider if the study provided useful information for categorization of the products as Category III or IV irritation hazards. Dr. Lehman-McKeeman responded that tests using rabbits would yield more compelling results, because this study identified only products that cause significant irritation. At this point, she believed the study data were insufficient to distinguish between Category III and IV. Dr. Fenske reminded Board members that they did not have information concerning how EPA distinguishes between Category III and IV substances. Although he agreed with Dr. Fisher's point that the study does not identify mild reactions, Dr. Fenske argued that the data do distinguish between moderate and mild irritation and the decision for how to use this information lies with EPA.

Dr. Fitzpatrick commented that the redacted information did not significantly interfere with the HSRB's review, with the exception of determining risk to subjects during the ethics review. She concurred with Drs. Fenske and Lehman-McKeeman, but argued that some questions were not answered, such as the relationship between dose and actual amount used, specifics concerning the formulation of the products, subject recruitment procedures, grading of reactions, and identification of the reaction graders. Therefore, she concluded that this report could not be considered a good example of such a study report because of the many unanswered questions. She also commented on the lack of rationale for the need for human studies and that AIRB procedures may be less than optimal.

Dr. Kim stated that although grading the reactions of exposure using a + or – designation is acceptable at the individual level; however, problems arise when an average of multiple subjects' reactions is used to classify the products. Given the proportion of subjects with definite erythema and a one-sided 95 percent confidence interval (CI), a reaction rate of up to 14 percent for one product and 16 percent for the other cannot be ruled out. He suggested that EPA may wish to consider different ways of categorizing such materials.

Dr. Fisher summarized that the absence of negative controls was not a significant problem, the data from the study were usable, and air-drying of the patches before application was not a fatal flaw. Considering the reversal of reactions, another way to analyze the data could be considered, but this also was not a significant flaw. The study cannot detect weaker reactions. A lack of blinding also may be an issue. Dr. Chadwick responded that blinding in this study design probably would not significantly strengthen the data because the incentive was to not find a reaction.

Dr. Chadwick requested clarification of the 30-minute drying procedure, asking whether the properties of the product change when the product is dried and whether the product was water soluble. Dr. Gardner replied that these matters were part of the sponsor's CBI claims. In his opinion, the characteristics of the product are not likely to change significantly when the product was dried. Dr. Lebowitz commented that he had concerns that volatile compounds could make the skin more susceptible to irritation; these compounds do not contact the skin in the study. He added that a negative control to determine that irritation was not caused by the patch would have been useful. Dr. Krishnan expressed concern about the approval of multiple products. He considered the issue of volatile compounds to be of less concern because such compounds volatilize quickly with normal use and are thus less likely to contribute to irritation.

Dr. Fisher summarized the discussion. She stated that negative controls would be desirable, but the data remain useful. There was no consensus among Board members concerning whether air drying would impact irritation. Dr. Fenske commented that this study resulted in 48 hours of skin contact with the test materials, which is significantly more contact than the average user would experience. Unless the volatile compounds in the product dramatically change the properties of the active ingredients, 48 hours of occlusion offsets concerns about these compounds. Dr. Chadwick argued that in the absence of other information, he remained unconvinced that the volatile compounds were not a concern. In response to a question from Dr. Fisher, Dr. Gardner speculated that any additional information he could provide might not suffice to conclusively resolve this issue.

Concerning the ability of the study to detect weaker reactions, Dr. Fisher stated that the results were inconclusive. If a positive reaction is not observed after 72 hours, and if the test was not designed to detect weak reactions, the Board cannot conclude that the study tested the full range of possible reactions. EPA will discuss this issue when deciding labeling language.

Ethical Considerations—48-hour Primary Dermal Irritation Study

Dr. Fish discussed the HSRB's ethics assessment of the study. She agreed with Mr. Carley's assessment and re-emphasized that this study would not meet current requirements. Concerning general ethical issues, the study used a convenient sample, which was appropriate. Board concerns regarding unfair inducement to the economically disadvantaged to participate were well addressed by TKL Research staff. The issues of confidentiality and use of Social Security Numbers also were adequately addressed.

Remaining concerns include enrollment of 54 subjects although the protocol called for 50; this would be unacceptable in academic research. Concerning payment, a lack of prorating

payment for those who did not finish the study is a concern. In this regard, TKL Research did not follow EPA guidelines for payment of research subjects. Other concerns include the non-payment to subjects for failing to follow protocol instructions, and the issue of "finder's fees" may have resulted in undue coercion to remain in the study.

The quality of the review by the AIRB also is questionable. The Board must assume that the AIRB had sufficient information to identify and weigh the risks of all substances used in the study. Another troubling issue is the language regarding treatment for research related injury only if it is "significant" and an "immediate" result of the study. The study met 40 CFR §26.1703 and did not enroll children or pregnant or nursing women. Dr. Fish agreed, with some misgivings, that there was no clear and convincing evidence of fundamental ethical flaws.

Dr. Philpott agreed with Dr. Fish. He emphasized his concerns about the AIRB review, including the independence of each member's activity, whether there was sufficient information about justification of a human study, and the lack of information regarding subject recruitment. Dr. Philpott stated that there were problems with the informed consent process, including use of verbal consenting, medical screening occurring before subjects signed the ICF, and the associated HIPAA waiver. He noted that these are matters that the AIRB should have questioned. Dr. Philpott noted that although a subject may have withdrawn from the study, the ICF indicated that their information may still be used. To preserve scientific integrity, the study design should compensate for possible subject withdrawal from a study. Dr. Fisher informed Dr. Philpott that under HIPAA regulations, researchers are permitted to use collected information even in the event of subject withdrawal. Dr. Philpott argued that the language on this ICF, which indicated that "all" information could be used, was too broad.

Dr. Menikoff agreed with the comments made by Drs. Fish and Philpott. He stated that the Board did not have resolution concerning the information the AIRB had on the other three products. The study was performed prior to establishment of the current rule and is not fundamentally unethical but is deficient. The failure to test the products on animals also could be considered a deficiency, because it is beneficial to initially test products on animals to detect serious adverse reactions, despite the possibility of obtaining better data from human studies. Dr. Brimijoin noted that although the Board does not know the identities of the tested products, they do know that the active ingredient is one of three that are currently registered and have been previously subjected to extensive animal testing. This particular formulation is new and did not undergo animal testing, but the active ingredient was tested. Dr. Menikoff countered that EPA requires new combinations of ingredients to be tested; therefore, animal testing should have occurred before human tests.

Dr. Fisher asked whether the language of the ICF adequately described worst-case scenarios. Irritation is listed as a worst-case event and described side effects included redness, swelling, peeling, and small blisters or sores—these effects are worse than those caused by a typical Category III product. Dr. Menikoff agreed that EPA regulations require minimization of risk to humans; therefore, the sponsors should have ensured no strong reactions in humans would occur. Dr. Brimijoin stated that WHO lists compounds that produce significant irritation in animals, but did not produce irritation in humans. Failure to test these products in humans could

result in the product being labeled with a more severe toxicity category. The intention of the sponsor was to confirm that the products did not cause irritation in humans.

Dr. Fisher summarized that the study was deficient relative to some accepted standards. The Board had concerns about the lack of willingness to prorate payment, the quality of the AIRB review, the language for treatment of research-related injuries, medical screening of participants before official entry into the study, and about inclusion of HIPAA information on the ICF. There were potential coercive elements to the study. The HSRB also found the justification for human versus animal studies lacking. Although these deficiencies are noted, the Board considers them unlikely to have resulted in serious harm. Subjects were adequately informed of risks during the informed consent process and the lack of prorating for participation likely does not reach the level of serious harm.

Dr. Menikoff added that the AIRB approval of subject exposure to the five compounds could have led to serious harm if the AIRB was not fully informed about the identities and/or risks of the compounds; this issue needs to be resolved. Dr. Fisher added that EPA staff had indicated that the AIRB was fully informed about all compounds tested.

Dr. Sharp requested clarification concerning whether the data were useful to EPA versus whether the study was necessary (or could animal studies generate equivalently useful data). Dr. Fisher answered that although this study may not be useful for identifying minor irritants, the Board cannot comment on whether the data are useful to EPA for determining its toxicity category. Dr. Chambers stated that human studies can be deemed necessary because many people believe animals should not be used to test products intended for use in humans. She asked whether it is possible for a registrant to receive a waiver from EPA to test products directly on humans. Mr. Jordan stated that the Board's deliberations have been useful for EPA understanding of the relative value of animal versus human testing for evaluation of irritation potential. At present, EPA does not have a policy on waiving animal studies; however, in the future, if a company wishes to test on humans a new formulation not tested in animals, but information is available on components and possible interactions, a waiver might be considered.

Repeated Insult Patch Test (RIPT) for Sensitization

Background

Mr. Jordan and Mr. Carley presented background information on EPA's review of the RIPT for Sensitization. This study tested the same products (products A and B) as those described for the 48-hour Primary Dermal Irritation Study. Sodium lauryl sulfate was included as a positive control. Products A and B are both repellents and contain the same EPA-registered active ingredient(s) and similar pesticidally inert ingredients. The two submitted study reports describe results for one of 15 or 16 substances tested in two parallel executions of the protocol using two sub-panels of subjects. The sponsor's three patches are reported to have remained in place for 48 to 72 hours; all others were removed by subjects after 24 hours. Both protocols used a single patch containing sodium lauryl sulfate as a "compliance check;" this reflects use of a known concentration of a weak irritant to ensure that patches were not removed early. All

subjects were non-pregnant, non-nursing consenting adults, free of skin disease, not sensitive to similar products, and not using medications.

Of 246 enrolled subjects, 210 completed the entire 6 weeks of the study. Target enrollment was 200 to complete the study. The test encompassed three phases. The induction phase involved nine consecutive applications of patches and readings of patch sites, occurring on Monday, Wednesday, and Friday over the course of 3 weeks. This was followed by a rest period of 10 to 15 days, and then by a challenge phase, in which identical patches were applied to naïve sites and read after 48 and 72 hours. During weeks 4 through 6 of the protocol, the subjects could miss application of one patch and receive a "make-up" patch.

Science Assessment

Dr. Gardner provided EPA's science assessment of the RIPT study. The goal of this study was to determine if the products in question cause skin sensitization. Skin sensitization data are required under 40 CFR Part 158 for registration of all pesticide products. Results of such studies indicated possible induction of allergic contact dermatitis from exposure of the skin to the test substance, and support precautionary labeling. Labeling is based on the sensitization potential of a product; a standard precautionary statement for a skin sensitizer is "Prolonged or frequently repeated skin contact may cause allergic reactions in some individuals."

EPA encourages minimization of animal testing. Although EPA does not encourage human sensitization testing, the Agency has sometimes accepted it in place of animal testing. The submitter is seeking a waiver of animal testing because the components of the tested products are discussed in published literature; have histories of use as intentional food additives or in cosmetic products directly applied to human skin; and are well-known to EPA. Skin sensitization tests with animals were reported in the literature for eight of the 12 ingredients in the two products (evaluated by the Buehler Test and Guinea Pig Maximization Test). The physical characteristics of two ingredients prevent direct sensitization testing. No published information was found by the sponsor concerning the remaining two ingredients; both occur in the products at low concentrations.

Skin sensitization (allergic contact dermatitis) is a delayed cell-mediated immune response, which begins with dermal exposure to a chemical. After absorption into the skin, a reaction with proteins in the skin must occur to induce the cellular processes of the immune response. Skin sensitization test methods include an induction phase when the capacity to respond to a challenge may develop. The standard test methods also include a challenge phase to determine if a test substance has sensitized the test animal.

Eligible individuals for this study included males or females who were at least 18 years old; in general good health; free of any systemic or dermatologic disorder which would interfere with the results of the study or increase the risk of adverse events; of any skin type or race, given that the skin pigmentation allowed discernment of erythema; had completed a medical screening procedure; and had signed an informed consent document. Excluded candidates included those who had any visible skin disease which would interfere with the evaluation; were receiving systemic or topical medication which would interfere with the study results; had psoriasis or

active atopic dermatitis or eczema; were pregnant, planned to become pregnant during the study, or were breast-feeding; and/or had a known sensitivity to cosmetics, skin care products, insect repellents, or to topical drugs related to the material being evaluated. The subjects were largely female and Caucasian.

The dosing method was similar to that used in the 48 h Primary Dermal Irritation Study. For the RIPT, 0.2 ml of each test material was applied to a 2 cm-by-2 cm Webril pad attached to a non-porous plastic film adhesive bandage. The patches were then air-dried for 30 minutes before application and secured with hypoallergenic tape. Patches were applied to the skin of the infrascapular area of the back, to the right or left of the midline, or to the upper arm.

The duration of the dosing is reported inconsistently. The protocol stated that all patches were removed by the subjects after 24 hours, but the ICF states that patches remain in place for 24 or 48 hours. There was no documentation of instructions to subjects informing them which patches to leave in place until their next visit. A letter to the AIRB explains that this is a "multi-sponsor" study with patches applied for differing durations. Upon request from EPA, the sponsor provided a supplement statement that the sponsor's patches remained in place for 48 to 72 hours, until the subject's next visit, and were removed by staff.

The system used for grading irritation response was the same as that used in the 48-hour Primary Dermal Irritation Study. The irritation responses noted in the RIPT are inconsistent with those observed in the 48-hour Primary Dermal Irritation Study. In the Primary Dermal Irritation Study, more than 50 percent of the subjects had a positive response 48 hours after application. In the RIPT study, less than 2 percent of subjects had a positive irritation response at any interval after patch application.

Irritation responses differ from sensitization in that they are localized and do not extend beyond the patch site. Irritation reactions also are usually reversible and are similar in the challenge and induction phases.

Results and Discussion

Mr. Carley presented the results of the RIPT. The data are presented in tables, and each square in the table represents one of nine induction phases. The numbers reported are the numbers of readings of each product at that point in time for the indicated level of irritation. Each page reports data for only one product. The data indicate that a subject reacted to both products in the induction phase as (++), and as (?) to both products in the challenge. In addition, two subjects reacted to both products in the induction phase as (?) and two subjects reacted to one product each in the induction phase as (?).

Mr. Carley described several sources of uncertainty. The patches were dried before application to the skin, which represents a different pattern of exposure from typical use of a topically applied repellent. The duration of exposure to the product is inconsistently reported. The results of this study are inconsistent with those from the 48-hour Primary Dermal Irritation Study. The study did not include control data adequate to ensure appropriate differentiation

between irritation and sensitization responses. All the subjects who responded were in Panel 1, which could indicate that readings may have been inconsistent between the two panels.

Based on this information, EPA concludes that the RIPT by itself cannot replace the required animal test of sensitization potential. Additionally, human experience with the components in cosmetics and foods, and the absence of skin sensitization in animal studies with most product components provide stronger evidence than this RIPT study to support the conclusion that the two products are not likely to be sensitizers.

Ethics Assessment

Mr. Carley presented EPA's ethics review of the RIPT. Applicable ethical standards include 40 CFR §26.1303 (defines standard for documenting ethical conduct of research), 40 CFR §26.1703 (forbids EPA reliance on research involving intentional exposure of pregnant or nursing women or children), and 40 CFR §26.1704 (forbids EPA reliance on research if there is "clear and convincing evidence" that its conduct was fundamentally unethical or significantly deficient relative to standards prevailing when it was conducted). The initial submissions did not address the requirement of 40 CFR §26.1303 to document ethical conduct. Resubmissions were adequate to support review; however, discussions of risk, risk minimization, benefits, and risk/benefit are weak, but acceptable for pre-rule studies.

The purpose of this study was to determine the ability of two experimental repellent products to cause allergic sensitization by application to human skin under controlled patch conditions. The sponsor's policy is to avoid "unnecessary use of animals in testing;" thus, these studies were submitted to support a request for a waiver of EPA's normally required animal testing for sensitization potential.

The study enrolled 246 subjects in two parallel panels; 52 subjects were male, 194 were female. The gender distribution was the same at both the beginning and the end of the study. The subjects ranged in age from 18 to 70 years, with an average age of 45 years. The subjects were largely Caucasian (178), and also Hispanic (54), Black (10), and "Other" (4). Of those enrolled, 210 subjects completed the study. The subjects were selected from people who had previously participated in research at this laboratory. The subjects received $110 in compensation for 13 visits, which EPA considers likely to attract primarily economically disadvantaged subjects. There was no other indication subjects were from vulnerable groups.

The risks for participation were described to subjects in generic terms (identically for both the primary irritation and RIPT studies). Identification of sensitizers before marketing and use has potential societal benefit, but the ability of this assay to identify weak sensitizers is unclear. If the results of this study are scientifically acceptable, the benefit probably justifies the incremental risks to subjects. The study was overseen by the AIRB, as described for the 48 hour Primary Dermal Irritation Study. The sponsors have submitted documents indicating that AIRB composition, procedures, and review meet regulatory requirements. A general compliance with FDA rules was asserted by TKL Research.

Written consent was obtained from all subjects, using a form approved by the AIRB. The ICFs were generic and sometimes unclear, especially in characterizing test materials and explaining 24-hour versus 48-hour patches. The consent process described emphasizes reliance on frequent test subjects, and on establishing their eligibility rather than their fully informed understanding. Regarding respect for subjects, subject privacy was not compromised in study reports. Subjects were paid only upon completion or if they withdrew for "personal reasons beyond their control," which may have unduly influenced subjects not to withdraw.

Ethical concerns for this study include recruitment of subjects from a population of frequent test subjects, without explicit consideration of representativeness; low compensation that might attract only economically disadvantaged subjects; and a compensation scheme tied to completion or withdrawal for an approved reason, which may have unduly influenced subjects not to withdraw. The ICF acknowledges possible lasting effects, but treatment is promised only to "relieve the immediate problem," and only for undefined "significant reactions." There was a troubling qualified promise to identify the agent inducing an allergic reaction. Subjects were also unnecessarily identified by Social Security Number.

EPA found some gaps in documentation of ethical conduct, but the study was relatively complete by pre-rule research standards. EPA found no clear and convincing evidence the research was fundamentally unethical and no intentional exposure of children or pregnant or nursing women. EPA has many ethical concerns regarding this work, but the research was consistent with common practice in testing of cosmetics and other consumer products not regulated as pesticides. There was no clear and convincing evidence the research was significantly deficient relative to prevailing standards.

The charge to the HSRB was to determine whether these studies were sufficiently sound, from a scientific perspective, to be used as part of a weight-of-evidence assessment to evaluate the potential of the formulations tested to irritate human skin and to determine if there is clear and convincing evidence that the conduct of these studies was fundamentally unethical, or significantly deficient relative to the ethical standards prevailing at the time the research was conducted.

Dr. Fisher requested clarification of the risks involved in a sensitization study compared to an irritation study. Mr. Carley explained that this study excluded individuals known to be sensitive; therefore, if a subject responds positively during the challenge phase, the subject has been made allergic to a component of the product. The chances of inducing an allergic reaction are much lower in a single dose study; the RIPT involves nine instances of exposure to the test products. Dr. Fenske questioned whether EPA seeks assistance from a dermatologist for evaluation of these types of studies. Mr. Carley responded that EPA did not seek such assistance.

Dr. Menikoff stated that these types of studies have been performed for many years, are regarded as valuable by industry, and are performed for regulatory purposes. Many perform this testing in addition to animal tests to confirm that their products are safe for humans. He disagreed that sensitizing people is a significant side effect of the RIPT. In this case, no subjects were sensitized during the study.

Public Comments

Dr. James Milbauer and Ms. Milena Reckseit of TKL Research

In response to a question from the Board, Ms. Reckseit explained that one screener was used to assess reactions in the RIPT study. The demographics and socioeconomic characteristics of the participants in this study are similar to those described for the 48-hour Primary Dermal Irritation Study. Concerning compensation, the ICF clearly stated that subjects would be paid $110 only upon completion of the study; however, if a clinician indicated that a subject must withdraw from the study, the subject was paid. Subjects who had a sound personal reason for withdrawing (i.e., car accident, death in the family) also were paid on a prorated basis. This practice also was followed for the 48-hour Primary Dermal Irritation Study, but was inadvertently not described in the ICF. Ms. Reckseit continued that the scientific integrity of the study would have been compromised if a large number of subjects withdrew. This prompted the clear statement that subjects would only be paid if they met the previously described conditions.

Dr. Menikoff requested clarification concerning the potential 48-hour patch application indicated in the ICF. Mr. Carley clarified that the sponsor's supplemental response to EPA questions indicated that this was a mixed sponsor study; some sponsors requested a 24-hour application, while others asked for 48 hours, despite indications on the protocol and study report that all applications took place for 24 hours.

Dr. Milbauer explained that the lower erythema ratings during induction were based on the 24-hour application, which could account for the inconsistencies between the RIPT and the 48-hour Primary Dermal Irritation Study. He added that two different graders were used for each test, although both were trained by the same dermatologist.

Dr. Philpott commented that subject #55 had evidence of a reaction during the induction phase. This subject's patches were exchanged for semi-occlusive patches and the subject proceeded to participate in the challenge phase. He asked whether this subject was considered to have been sensitized to the product. Dr. Milbauer answered that because the subject did not react after the challenge, the subject is not considered to have been sensitized.

Dr. Philpott expressed concerns with the conditions for payment, stating that these conditions were coercive. He also questioned whether the AIRB had reviewed the telephone script. Ms. Reckseit explained that because the study is an IRB study, she assumed that the AIRB had reviewed the script, but was not certain.

Dr. Fenske returned to the issue of sensitization. Products A and B have similar active and other ingredients. He questioned whether challenge on another part of the skin with a given product leading to a reaction is the effect of product A induction or the effect of the multiple patches tested. Dr. Milbauer answered that sensitization is a specific reaction and occurs in isolation. It is possible that a person could develop sensitivity to one ingredient, and, upon challenge, would develop sensitization at both sites. If this occurs, separate ingredient testing

could be performed. Dr. Fenske asked if a positive rating upon challenge would be considered positive for sensitization. Dr. Milbauer confirmed this.

Dr. Carriquiry inquired how the criterion of 200 subjects had been determined and who had determined it. Ms. Reckseit responded that she did not know who made this determination or how it had been made. TKL Research's role in this study was to recruit subjects. Dr. Fenske clarified that TKL Research recruits, consents, screens, and performs the test, and asked who performed the power calculations to determine sample size. Dr. Milbauer explained that this protocol was written by TKL Research and power calculations were determined by a staff statistician. A sample size of 200 subjects is considered typical for studies of this type. Dr. Carriquiry countered that the term "typical" was imprecise. In a study review, she expects to see the calculations used to determine a need for 200 subjects. Without this information, the Board has no way of assessing whether this sample size is excessive or does not have adequate power. Dr. Fisher questioned whether any data were available concerning the demographics of those who withdrew from the study. Ms. Reckseit indicated that she did not have this information.

Dr. Chadwick asked for further clarification of the authorship of both protocols. Dr. Milbauer answered that one primary investigator for the protocol is a dermatologist; the other is a dermatologic safety person. A medical writer and statistician also contributed to the protocol.

Dr. Lebowitz asked whether the compounds used in this study were tested prior to the study to determine that they were not adjuvant to sensitization. Dr. Milbauer responded that this information was determined in preclinical reviews by the sponsor and provided to EPA.

Dr. Fisher questioned whether the AIRB had reviewed information for all patches used in the study, given that there were multiple sponsors for the different patches. Dr. Milbauer answered that the other patches contained cosmetics and IRB approval is not required for cosmetics. Dr. Fisher requested clarification that the ICF for testing products A and B also indicated that participants were obligated to have the other substances applied to their skin, but the AIRB did not have information on these materials. Dr. Milbauer clarified that the AIRB had been informed that the other substances were cosmetics. Dr. Fisher commented that this protocol likely would not have been approved if submitted under the new rules.

Dr. Philpott questioned the use of sodium lauryl sulfate as a control to assess compliance and asked how this was done and if sensitization was observed. Dr. Milbauer explained that this substance causes irritation, not sensitization.

Board Discussion

Scientific Considerations—RIPT Study

Dr. Fisher commented that an issue for the scientific review is to determine whether the study produces useful data. The answer to this question will impact the ethics review.

Dr. Zhu began the science review. Concerning demographics, the gender composition was uneven and the sampling scheme was likely to have led to a non-representative sample. The study protocol called for switching subjects from an occlusive to semi-occlusive patch (or to switch the patch to a new site) if the subject showed irritation of more than (++). The results of the study indicate no positive reaction to the products. Dr. Zhu cautioned that if subjects withdrew from the study for reasons associated with their reaction to the patches, ignoring the data from these subjects would lead to bias. If attrition is due to random reasons (i.e., the subject found participation to be inconvenient), this will reduce the statistical power, but not bias the results of the study. The data for this study indicated that there were no positive reactions among those who withdrew.

Dr. Zhu considered the results concerning subject #55 to have been downplayed. These results were not reported in the summary statistics; therefore, the number of positive reactions was under reported. This subject appears to be allergic or sensitive to the patch. Information on subsequent reactions was missing from the report for product B, but Dr. Zhu speculated that subject #55 was sensitive to both products. Dr. Fisher questioned why, given the exclusion criteria, a subject was not excluded if found to be sensitive during the indication phase. Mr. Carley clarified that the criteria are applied before the study begins. Dr. Zhu added that the study protocol specifies termination only if the subject experiences a serious adverse event. Dr. Lebowitz cautioned Board members against confusing multiple times of irritation with sensitization. Irritation does not necessarily imply that a humoral response through hypersensitivity occurred. Dr. Philpott commented that his assessment of this data indicated that the irritation was residual at the original induction site after removal of the original occlusive patch. Dr. Zhu disagreed and noted a footnote indicating that data for this subject, after switching the patch to a different site and changing patches, were reported in a different table.

Limitations to this study included use of a single rater for observations, which could lead to variation or error in readings. No information was available on dose or mixture; decisions regarding this issue need to be made by EPA. The study population also may not be generalizable. If subjects have participated in multiple studies with TKL Research, they may be more likely to develop resistance (or sensitivity) to chemicals with similar structures. The study participants were mostly female, and males and females may have different sensitivities to the products. Concerning data analysis, the conclusion of “no evidence of sensitization” ignores the response of subject #55.

Dr. Zhu recommended considering multiple raters to independently evaluate each subject; statistically quantifying the chance of meaningful (timed) patterns of positive reactions of the same subject; developing standards for data reporting and analysis in accordance to repeated outcome data (i.e., do not ignore attrition and consider the subject as a unit of analysis, as well as the data point); and requiring analysis that differentiates outcome of a susceptible sub-population (incidence of severe reaction) from the average.

Dr. Fenske commented that EPA indicated in its review that there were concerns with this study, given that the components of the products have already been marketed and people already have been exposed to them. This may have led to more subjects showing signs of sensitization, but this was not the case. Concerning the evaporation of solvents, Dr. Fenske

indicated that he was comfortable with the rationale for allowing the materials to dry on the patch before application and did not believe this approach negatively impacted the study results. Regarding the scoring system used, the European Commission has clear guidance for 48-hour primary irritation tests, but Dr. Fenske was unsure if such guidance existed for the RIPT for sensitization. The report does not provide sufficient information to determine if this is a standard method for scoring. Given the substantial amount of data from animal testing of these products, it was predictable that any sensitization reaction would be weak. EPA believes that this study is less able to identify weak reactions than are animal studies. This implies that EPA found the animal data to be adequate and this study did not contribute significantly to the knowledge base. The duration of exposure was inconsistently reported. The protocol and study report indicate removal of patches after 24 hours and examination after 48 hours, but there is ambiguity in the supplemental materials concerning this issue. The duration of exposure should be clarified. Dr. Fenske addressed concerns about inconsistencies with the 48-hour primary irritation study. Less irritation would be expected for this study, because patches were applied for only 24 hours. There was no control data to differentiate between irritation and sensitization; the sodium lauryl sulfate control patch was used to assess compliance. There was insufficient justification for the sample size.

The reports lack a startling amount of detail concerning the results of the study, which are limited to two sentences within the report (further information is reported in the Appendices). In general, studies of this sort are not required; rather, their purpose is to add a level of confidence in the safety of a product that many consumers will use. Manufacturers wish to avoid product recalls, which are deleterious both for them and for the public. The Board's critique implies there was no good reason to perform this study; however, additional confidence in product safety may be a good reason. Dr. Fenske stated that he was not averse to human studies, if they are carefully designed. This study included appropriate protocols to detect irritation during induction and procedures to limit such irritation (use of semi-occlusive patches, applying patches to new locations).

Dr. Fitzpatrick stated that the study report required more detail concerning why the study was performed on humans, justification of dose and sample size, how subjects were chosen, and discussion of the representativeness of the sample. The results and analysis are lacking, as is information concerning who performed irritation/sensitivity rating and their qualifications.

Dr. Carriquiry stated that she disagreed with Dr. Fenske and believed that this study was not carefully designed or implemented. The Board cannot determine whether the sample size was adequate, but the sample itself was not representative. Confounding of cohort location and raters occurred and thus the cohorts cannot be compared. This is an artifact of having only one person score the first reaction and a different person score the second. EPA should find no use for these results. There was no information concerning the demographics of those who withdrew from the study, although it is likely that they did not withdraw because of reaction issues. The study included no statistical analysis whatsoever. This data cannot conclude that the products do not cause sensitization.

Dr. Brimijoin requested clarification of "sensitive" versus being "sensitized" and added that the criteria presented to indicate "sensitized" were not satisfactory. When a challenge is

administered after the rest period to a naïve site, a reaction must be seen to conclude that sensitization occurred. By these standards, subject #55 was not sensitized. Dr. Lebowitz explained that sensitization, encompassing delayed-type hypersensitivity reactions are obvious; he was certain that no subjects were actually sensitized to product A or B. Dr. Fish questioned whether the obviousness of a sensitization reaction means that the issue of inter-rater reliability is less serious. Dr. Lebowitz said that this was a true statement. A dermatologically trained observer can easily distinguish a sensitization reaction from irritation.

Dr. Carriquiry inquired, given the sample size, how often sensitization might expect to be seen. This information should drive the determination of sample size in such studies. Dr. Zhu commented that although he understands the clinical definition of sensitization, he believes immunological testing would be needed to determine sensitization because observation was not sufficient due to the different exposure conditions. Dr. Lebowitz explained that a person who has been sensitized exhibits a characteristic delayed-type hypersensitivity reaction to a lower dose upon challenge. He added that historically, the U.S. government could not decide whether formaldehyde was a sensitizer, given that approximately 1 to 5 percent of those exposed to it develop sensitization. There is disagreement among the United States and other countries concerning whether a 1 to 5 percent rate of sensitization is sufficient to deem a substance a sensitizer.

Dr. Fisher summarized that the Board concluded that this report was of poor quality, and the use of single raters was not optimal. There was no rationale for the number of subjects included in the study, which is a weakness for interpreting the results and their meaningfulness. Confounding among cohorts and raters occurred. There is no evidence concerning whether the study was well-implemented or not, but it was carelessly reported. Dr. Fenske countered that the report provided a great deal of information, but not in a user-friendly format. He considered the protocol to have been generally well planned and executed, and employed appropriate safety measures.

Dr. Fisher inquired if EPA had received resolution to its questions concerning dosing, which was reported inconsistently. Mr. Carley agreed that duration of patching was reported inconsistently. If patching did take place for only 24 hours, this might explain the inconsistencies between the results of the primary irritation study and the RIPT. Dr. Fisher commented on the lack of differentiation between irritation and sensitization. Dr. Lebowitz agreed that there was no control for this, but this is not relevant for distinguishing sensitization. Dr. Fisher commented that the readings appeared inconsistent and that this could be related to the issue of using only a single rater and lack of a negative control. The sample was not representative, but it is unknown whether this would have affected sensitization rates. Dr. Fisher stated that there appeared to be no evidence of sensitization. The study design is sufficient to assess sensitization, but whether the population is representative and the sample size adequate is questionable.

Dr. Fisher commented that confirming in humans what is known in animals is admirable, but the Board is unsure whether this study contributes to EPA's knowledge base. Dr. Lebowitz stated that given his experience with sensitization reactions, he would want to know that sensitization was not observed in animal models before testing for sensitization in humans.

Dr. Fenske reminded Dr. Lebowitz that animal studies of individual ingredients had been performed. Dr. Lebowitz countered that it was unclear if animal studies had been performed using these particular combinations of ingredients. If such studies have not been performed, the investigators could not conclude that the ingredients would not synergize to create sensitization in humans.

Dr. Fisher concluded that sensitization was not observed in this study, but there was a rationale for testing in humans. The sample size and the representativeness of the sample were questionable; the report was poorly written. At this point, the Board cannot conclude whether the study will contribute to EPA's knowledge base concerning products of this type.

Mr. Carley clarified that he had received indication from the sponsor indicating that the patches remained in place for 48 hours, in contrast to what was reported in supplemental materials. The ICF permits patches to remain in place for 24 to 48 hours, and in some cases 72 hours, if the patch is applied on a Friday. The IRB questioned this, and the response from TKL Research was that the study was a multi-sponsor, multi-substance test, necessitating different durations of exposure.

Dr. Brimijoin commented that although there was no rationale for the study population composition, the characteristics of this population appear reasonable. Women and children are most likely to use insect repellents.

Ethical Considerations—RIPT Study

Dr. Fish opened discussion of the ethics of the RIPT study. She stated that the Board cannot judge whether there was sufficient animal data on sensitization provoked by these products to support human studies. The issues of subject compensation and prorating of payment are similar to those from the primary dermal irritation study, ameliorated somewhat by clarification by Ms. Reckseit that the explanation of prorating payments had been inadvertently omitted from the ICF. Dr. Fish expressed concern that subjects who chose to withdraw would not be paid, which could be construed as coercion to remain in the study.

Dr. Fish also expressed concern about the AIRB. The ICF presented to the AIRB was generic and nonspecific. The section describing risk is the same as that on the ICF for the Primary Dermal Irritation Study, but risks associated with sensitization would seem to be higher than risks associated with primary irritation. The statement concerning treatment for injuries is vague, as was the case for the Primary Dermal Irritation Study. Dr. Fish expressed concern that the AIRB only had information for products A and B, and not for the other products that would be applied to the subjects. The telephone script for recruitment refers to "testing fragrances," which seems deceptive. Mr. Carley clarified that there were two telephone scripts, one of which included mention of repellents.

Dr. Sharp commented that all human studies could trouble ethicists, because humans are being placed at risk to further corporate interests. The idea of human testing as an alternative to animal testing is troubling. Researchers should never expose humans to risk when alternative testing methods are available, unless there is a significant benefit to human testing. The moral

consensus is that all risk should be minimized, which implies that animal testing should always occur first; it would be fundamentally unethical not to do so. The 246 volunteers in this study may have needlessly been placed at risk. Dr. Fisher clarified that to declare a study "fundamentally unethical" there must be evidence of intent to cause serious harm or failure to obtain informed consent. Other Board members disagreed, considering "fundamentally unethical" to include, but not be limited to, these acts. Dr. Fisher thanked these Board members for the clarification.

Dr. Chadwick commented that for corporate sponsors who have a reputation of not testing on animals, asking them to do animal testing is akin to asking a vegetarian to eat meat; it conflicts with their own moral standards. In some cases, it might be reasonable to ask humans to participate in testing. In this case, the quality of the protocol and specificity of risk raise questions about the underlying science. Dr. Chadwick described his concerns, including the 30-minute drying period before application, the apparent lack of consent for medical screening, and the lack of detail in the protocol about the risk of sensitization. He stated that the procedures followed by the AIRB give the impression that this IRB is not compliant with EPA, FDA, or DHHS practices. When an IRB reviews a study that will be used by EPA for regulatory purposes, the IRB should follow EPA regulations for these studies. Mr. Carley reminded Dr. Chadwick that at the time this protocol was developed and implemented, EPA rules concerning human subject protection did not apply to third-party data.

Dr. Chadwick continued his analysis, asking whether the consent obtained using the ICFs described for this protocol were valid. It is questionable whether participants understood the procedures, risk, purpose of the study, and possible benefits. The ICF did not describe research procedures. Dr. Chadwick added that he also was troubled by the phrase "sodium lauryl sulfate was used for control comparison." Sodium lauryl sulfate routinely is used as a skin irritant, and it appears that subjects were not adequately informed of this. Concerning payment, there are ways to use payments, prorating, or bonuses to ensure compliance that are not coercive. The procedures used in this protocol indicate a lack of understanding of this issue on the parts of the AIRB and TKL Research. The lack of a plan for informing subjects about potential sensitization reactions also is a flaw. The use of HIPAA language is a confounder in this study. Dr. Chadwick concluded that the AIRB and perhaps TKL Research are content to use a generic ICF instead of individual ICFs for each protocol. This practice violated ethical and regulatory standards and raises concerns about the quality of consent.

Dr. Fisher definitively stated that the consent was either significantly deficient or fundamentally unethical because the AIRB had no information about materials used in the study, other than products A and B; therefore, subjects were not informed about the study's risk. Therefore, there is no informed consent if the AIRB cannot determine the nature of the risk. Dr. Fenske countered that the other materials used were cosmetics that were registered and did not require IRB review because they are considered safe for human use. Dr. Fisher remarked that the TKL Research representative stated that the AIRB did not consider any information concerning the other products, considering them to be outside their purview because cosmetics are not subject to IRB review. Dr. Fenske commented that the Board cannot conclude that the products were hazardous and the subjects were deliberately misled. Dr. Fisher agreed, but repeated her opinion that the subjects were not informed because the AIRB did not have all the

necessary information. Dr. Fenske stated that TKL Research knew the identity of the other products and may have told the AIRB that these products were cosmetics that did not require IRB review. Dr. Philpott requested clarification concerning the information submitted to the AIRB. It appears that the AIRB was informed only about the repellents, but approved the ICF without information on the other materials used. Dr. Fisher reiterated that if an IRB does not have all necessary information, it cannot do its job. From an ethics perspective, there is no informed consent because the IRB could not complete its review. Dr. Krishnan asked whether EPA had information on the other products. Mr. Carley responded that EPA does not have this information, and it is not clear from the ICF whether subjects were told the exact number of patches they would receive or what the patches would contain. The duration of exposure also was not clear on the ICF.

Dr. Fisher concluded that the failure of the AIRB to review all materials fits the idea of lack of informed consent. The Board's consensus was that there was clear and convincing evidence that the study was significantly deficient regarding ethics. She added that this was the first protocol with supplemental CBI claims that the Board reviewed, and commented that the flaws in the protocol were not related to the CBI claims. Overall, the process for review of protocols with CBI claims proceeded smoothly. Mr. Carley agreed that the process worked well in this case, because of the scope of the claims. Reviews of other protocols may be more problematic.

Dr. Chambers commented that it would be unethical to force companies with philosophical objections to animal research to perform animal testing. Additionally, there is merit to exposing a small group of people to risk before exposing large populations to risk when the product is marketed.

Draft Framework for Developing Best Practices for Recruiting, Screening, Informing, and Obtaining Consent from Human Subjects of Occupational Exposure Studies with Pesticides

Mr. Carley presented EPA's draft framework for best practices for occupational pesticide exposure studies. The goal of this exercise is to develop a process to interpret the provisions of the rule requiring documentation of informed consent and application of the rule to the specific circumstances of occupational pesticide exposure studies. The framework will help define a structure for compilation of best practices for occupational exposure studies such as agricultural handlers' exposure, non-agricultural handlers' exposure, and re-entrant worker exposure (re-entrant workers enter areas that have been treated with pesticides). Major concerns for these studies include ensuring equitable subject selection, fully informed choice to participate, fully voluntary choice to participate, and respect for prospective and enrolled subjects.

IRB approval of research requires equitable selection of subjects, which considers the purposes of the research and the setting in which the research will be conducted. The investigators should be particularly cognizant of special problems when research involves vulnerable populations. Equitable subject selection requires fair distribution of research risks, assessment of which should consider the representativeness of the sample, appropriate use of inclusion/exclusion factors, special considerations for vulnerable populations, and appropriate

recruiting strategies. To meet the requirement of representativeness, an ideal sample would be derived from random selection of subjects from the target population of concern; this will help ensure broad applicability of research results and greater potential societal benefit. Representativeness of the sample thus is a crucial element for justification of the research. Representativeness can be maximized by identifying and characterizing the appropriate target population, defining the sampling frame relative to the target population, selecting a sample from the frame that preserves representativeness of the target population, and ensuring that the sample serves the scientific purposes of the research and has not been chosen for convenience.

Appropriate exclusion factors for these studies protect potentially vulnerable populations, including children, pregnant or nursing women, and prisoners. Inclusion factors to preserve representativeness include speakers of English and other languages, and both men and women. Special concerns for occupationally exposed populations include limited English skills, subordinate relationships to decision makers, and being an employee of the entities cooperating with the research or of the investigators or sponsors.

Recruiting strategies should be tailored to the purpose and design of the research to ensure equity and representativeness, offer candidates the opportunity to express interest in participating, and provide appropriate recruiting material for IRB review. Fully informed consent, i.e., knowing consent was obtained without undue inducement, force, or coercion and using a process in which the subject has sufficient information to make decisions about participation, is required. All ICFs must be signed by both subjects and project representatives to ensure that the consent process is complete and appropriate, subject participation is entirely voluntary; it also ensures that the subject has read the information provided, has had a chance to discuss the information and ask questions, and has been notified of the freedom to withdraw.

Next steps in developing the framework include refinement of the draft framework based on the HSRB discussions, solicitation of comments from stakeholders, populating the framework with best practices, establishing a process for ongoing maintenance of the framework, and making the best practices guidance widely and easily available.

The HSRB is asked to consider and identify any additional elements that need to be addressed concerning recruiting and enrolling subjects in handler exposure research, and, for each element of the framework, identify additional sources of guidance that could be useful for an investigator who is designing a process for recruiting and enrolling subjects in handler exposure research.

Dr. Fitzpatrick inquired if the short form for consent could be used. Mr. Carley responded that this form could not be used because of concerns about obtaining fully informed consent from people with low English skills. Dr. Menikoff commended Mr. Carley and EPA on the quality of the draft framework. He agreed that more specifics concerning some issues are needed. The subjects likely to enroll in these studies are likely to be considered “vulnerable” in a number of ways—socioeconomic status, immigration status, and English skills. Questions must be developed to ensure that participation is entirely voluntary. Mr. Carley agreed, and added that EPA expects that answers to questions will differ given the contexts (i.e., agricultural handlers versus non-agricultural handlers) because of different complication factors.

Dr. Menikoff raised the issue of ensuring workers are not penalized for not participating in the research. Much of this research will take place at employment sites and the research will be tied to work situations. The workers face the risk that they will be vulnerable to losing money or suffering other consequences in the workplace for failure to participate. There need to be clear rules to forbid this and procedures in place to ensure that it does not happen. Dr. Menikoff described an example of this situation. A farmer could agree to allow one of his fields to be used in research involving sprayed pesticides. This could result in the pilot who applies the pesticide being forced to work with a different substance than the pesticide normally used. The choice of the pilot to participate may not be entirely voluntary; if the pilot declines to participate, he could face a significant financial penalty by not performing his usual job. The Board discussed whether they would try to develop specific answers for specific situations such as this one, or develop general principals. Dr. Fisher asked the Board to consider a situation such as this in an ethical framework, for example, is the pilot being forced into a coercive situation. Dr. Menikoff stated that the general question for this situation was whether people do not receive their usual pay if they choose not to participate, and if this is acceptable. Dr. Fisher agreed that the guidelines should ensure that no one should be deprived of expected pay because of refusal to participate in research. She continued that specific issues to be addressed for this situation include whether the pilot would apply the usual pesticide with no measure of exposure, or whether additional risk could be incurred by applying a different pesticide. Dr. Menikoff stated that the general principle should be that no one should be worse off as the result of a study. Workers should receive their usual pay and not be forced to expose themselves to risk. Dr. Fisher agreed that the general principles should be that people 1) should not be worse off and 2) should not feel coerced to be exposed to something to which they normally would not be exposed.

Dr. Lebowitz commented that although this document must focus on EPA needs, it may be helpful to consider rules or regulations from other agencies, such as OHRP and FDA. Certain areas were emphasized by Mr. Carley in his presentation of the framework. Minimization of risk is paramount and there should be discussions to develop approaches to risk minimization applicable to subject recruitment and retention. Concerning avoidance of members of vulnerable populations, Dr. Lebowitz explained that in biomedical research, it is essential to include members of these groups, when not excluded by statute, to ensure representativeness. In the case of the occupational exposure studies, stratified random samples may be needed to allow appropriate conclusions to be drawn. Any lack of representativeness should be treated in analysis to determine any bias affects on the research conclusions. In his opinion, investigators must make an effort to ethically include members of vulnerable groups, perhaps by employing translators or writing ICFs in languages other than English. Dr. Lebowitz remarked that this research may have a potential future benefit to individual workers by improving assessment of exposure risk. Best practices must include assessment of study design, exposure, statistical analyses, measures of biological response, and other scientific issues.

Dr. Kim addressed scientific issues. Exposure studies will involve sampling that differs from other studies and there will be problems with calculating sample size. Community-based participatory studies in clinical settings may provide suggestions for addressing this. Dr. Sharp agreed that the idea of community consultation should be developed for the exposure studies.

Dr. Sharp continued that exclusion of children and the decisionally impaired from the exposure studies may impede progress to improve public health. Dr. Fisher noted that it is illegal to enroll children in non-observational pesticide studies. Mr. Carley agreed that because these studies involve intentional exposure, children cannot participate. Drs. Fisher and Sharp discussed the definition of "intentional exposure" versus "observational" and agreed that this would be discussed further at the June 2007 HSRB meeting, with input from EPA.

Dr. Sharp continued that he would like to further discuss the risk created by observation of pesticide application—what is the role of the investigator if he observes improper or illegal application procedures. Concerning the language and tone of the document, it is likely that many potential subjects will be Spanish speakers. He suggested that both English and Spanish speakers work in the consent process to help ensure fully informed consent of Spanish-speaking subjects.

Dr. Fisher commented that the Board should discuss risk-benefit balance. To be ethical, a study must have social or scientific values. The definition of "benefit" should be established, and could include social value. Dr. Lux reminded the Board that the draft framework focuses on recruitment, not study design. Mr. Carley explained that at the January 2007 SAP meeting, study design and methodology were discussed, but were treated as scientific issues for protocol design. These discussions revealed the need to discuss the best ways to recruit and obtain informed consent for the occupational exposure studies. Dr. Fisher indicated her understanding of the limitations of this document, but stated that benefit is nonetheless an important issue. Mr. Carley remarked that EPA does inform sponsors of the scope of EPA concerns. Dr. Philpott agreed that lack of recognition of the importance of the study design could hinder equitable subject selection; subject selection is difficult if questions and applicable populations have not been defined beforehand. Dr. Menikoff suggested that, at the outset of the document, the Board could comment that this document specifically addressed recruitment, but information on design also is needed to ensure recruitment is ethical.

Dr. Philpott addressed the issue of enrollment of the decisionally impaired. He recognized that even if a study is ethical and answers important questions, there may be state level issues that supersede the protection guidelines of the study. For example, there may be situations for occupational exposure studies that permit inclusion of people who can only consent by proxy; this would not be allowed in New York State, which has no proxy law for non-therapeutic research. Dr. Fisher noted that investigators are alerted to state and local laws that may be more stringent than EPA requirements. Dr. Menikoff commented that it is unlikely that decisionally impaired people will participate in exposure studies, but this issue does give guidance for considering the representativeness of the study.

Dr. Fisher addressed the complexity of consent materials. ICFs can easily overwhelm potential subjects, thus, to be ethical, ICF materials should be well written and undergo careful editing to eliminate ambiguity. Mr. Carley noted that sponsors must send EPA their protocols before implementing the study.

Dr. Hoel's comments related to both exposure and effect studies. He noted that there is increasing scientific interest in deoxyribonucleic acid (DNA)-environment interactions, which

gives rise to questions concerning the ethics of collecting genetic materials. He agreed with Dr. Lebowitz that stratification of sampling may be needed to ensure representativeness. He expressed curiosity about the exclusion of children from exposure studies, given that in the past he has performed motor and neurodevelopmental testing on children whose mothers may have been occupationally exposed to pesticides—this could not be done under strict rules excluding children.

Dr. Hoel addressed the lack of discussion of inclusion of labor unions. Unions serve as advocates for workers, and may help represent and explain the research and improve participation by the workers. Regarding expression of interest in the research, he cautioned that bias may occur because of self-selection by workers for participation. He added that exposure studies may also include work in developing countries and EPA must be aware of potentially less protective research regulations in those countries. Mr. Carley explained that if EPA uses the data, the Agency must review the protocol, regardless of where the research is performed. Dr. Fisher added that OHRP states that U.S. standards must apply internationally, unless the host country has higher standards; at a minimum, equivalent protection must be achieved.

Dr. Chambers stated that although science should not compromise ethics, there must be an acknowledgement that in some cases ethics may compromise science. For example, subjects withdrawing from the protocol before completion will result in censored data. If the EPA seeks true representativeness of studies, only large farms with many workers will be able to participate. It may be challenging to ensure scientific parameters, such as complete data sets and representativeness, and maintain ethical requirements. Dr. Fisher responded that this balance has always been an issue. There are ways to balance science and ethics to ensure that studies are both scientifically valid and protect subjects' rights.

Dr. Fenske noted that the framework document was well designed. The scope of the document was adequate when considering the recruitment, screening, and informed consent processes, but he expressed concern that the workers did not appear to be involved in the process. The process is driven largely by registrants and employers, but members of the workers' communities will be best able to communicate with other workers and assist researchers. A community-based participatory research model should be considered, because engagement of the community is important for exposure studies. Concerning exclusion of children, the National Institutes of Health requires that children under 21 years of age must be included in human research unless there are scientific and ethical reasons not to do so. A substantial portion of the agricultural worker population is under 21 years of age. They are the most at-risk members of the population because of a lack of education and a propensity for risky behavior. It is legal to handle pesticides at 16 years of age. Dr. Fisher asked Mr. Jordan if EPA had exceptions for inclusion of emancipated and mature minors. Mr. Jordan responded that EPA defines "child" as younger than 18 years of age. He clarified that EPA does not allow participation of people younger than 18 years of age in research involving intentional exposure. People of all ages can participate in observational research.

Dr. Fisher asked Board members to review Dr. Chadwick's draft of Board recommendations for the Best Practices Framework.

Day 3 Introduction

Dr. Fisher introduced the day's topics, including clarification of issues concerning the AHETF and AEATF protocols, EPA's need for new research on occupational handler exposure, and a review of the EPA FIFRA SAP January 2007 report, "Worker Exposure Methods."

Dr. Fenske recommended a modified agenda that would maximize Board discussion of the AHETF and AEATF protocols and the FIFRA SAP report. He noted that the EPA written materials documenting the need for new research on occupational handler exposure had made a convincing case and that less discussion might be required for that topic, with more time devoted to the SAP recommendations and Board discussion. Board members agreed with Dr. Fenske's suggestions.

Dr. Fisher suggested that it might be helpful at this juncture in the meeting to remember the points that the Board had raised regarding the AHETF studies in its June 2006 report. Dr. Fisher provided a summary of the major recommendations from that meeting. She noted that in that report the Board considered the occupational handler exposure monitoring studies, which were described as components of a large-scale exercise to create a database on occupational exposure to agricultural pesticides, to be largely worthwhile for quantifying and improving understanding of the exposures and risks to pesticide handlers. Although the potential benefits of this exercise were deemed to be significant, and the risks relatively modest, the Board found that the materials supplied for HSRB review did not adequately address risks and benefits. The protocols reviewed could not be properly evaluated for scientific validity for a number of reasons. The HSRB found the protocols to be lacking in sound rationales for how data generated by a given protocol would address the EPA's need for new data. The protocols lacked clear and appropriate plans for handling data, including statistical analyses. For example, a meta-analysis was proposed that would include studies with one subject to represent a particular pesticide and use context. A meta-analysis seemed inappropriate, and neither the sponsors nor EPA could provide an appropriate alternative statistical design for data analysis. Also lacking were clear explanations of how the data would be used. The HSRB understands that the data will be used to create reference points, which underscores the need for well-planned studies and good quality data.

At its June 2006 meeting, the Board recommended additional validation studies such as laboratory-based removal efficiency studies or field-based biomonitoring studies to determine the extent to which dermal exposure measurements may underestimate true exposure. The Board also recommended publishing the results of such studies in peer-reviewed journals and to inform and encourage participation of both the scientific and labor communities. Greater participation likely would improve the quality of the database and enhance its credibility.

The Board also recommended that a heat stress management plan be designed to include specific criteria for withdrawal from the study because of heat stress. The protocols should represent, as closely as possible, the conditions of a true work day and should document the reasons for and proposed duration of the study. The protocols also should include plans for the proposed number of subjects and plans to manage subject withdrawal—power analyses and statistics will be needed.

The Board commended EPA's response to its questions regarding use of diazinon in the AHE37 protocol. The Board understands that the Agency will require AHETF to identify a pesticide other than diazinon to use in this protocol to assess exposures associated with open pour activities, and that EPA will ensure that future protocols comply with the most current risk mitigation measures.

Public comments from several members of the AHETF at a previous meeting addressed some of the Board's concerns, namely the documentation and process of subject enrollment, appropriate alternatives to participation, and adequate compensation of participants for study-related injury; however, the Board did not consider that questions concerning adequate minimization of risk to study participants were adequately addressed. Participants in these studies may be exposed to higher levels of pesticides than they are during their usual work duties; this should be mentioned in the protocols. The protocols also failed to detail proper subject use of the pesticides and failed to address educational issues arising when subjects do not speak English. Study investigators also should consider providing subjects with the results of the study.

The HSRB considers the likelihood of heat-related illness to be a significant matter for the protocols. Many of the studies will require participants to wear what is essentially long underwear while working in high temperature environments. The protocol needs clear stop criteria, clear descriptions of the symptoms of heat stroke in the ICF, and a clear plan for reporting any heat-related illnesses.

Because some agricultural workers may be undocumented immigrants, maintenance of strict confidentiality is paramount. Additionally, investigators should be aware that undocumented workers may be reluctant to report adverse events, such as heat-related illness. The Data and Safety Monitoring (DSM) plan must be sensitive to this issue. Development of recruitment and ICF documents also must consider potential problems related to worker immigration status.

Board Discussion

Dr. Menikoff commented that the key goal of this research, in terms of how the studies are designed, is risk minimization. He added that it can be difficult to distinguish between "intentional exposure" and "observational" research. Subpart B clarifies the extent to which investigators cannot change what a person experiences—this leads to questions concerning whether these studies can be performed using workers who are already using the compounds as part of their work activities. He stated that the protocol should provide more information on ways to perform the study that do not alter the identities of the pesticides that are applied or the ways they are applied. Dr. Fisher responded that if handlers will be asked to use pesticides or wear clothing that increases risk beyond their usual risk, a risk management plan is crucial. This also relates to the issue of whether recruitment is truly voluntary. Risk minimization related to changes in use or exposure must be assessed. Dr. Lebowitz commented that the Board was at a disadvantage, having not yet seen the revised AHETF protocol referred to in the FIFRA SAP minutes. He also recommended that staff from EPA's Office of Research and Development

should be invited to the June 2007 HSRB meeting to provide further input on the distinction between observational and intentional exposure research and other issues concerning exposure.

Dr. Fish stated that although scientific considerations are of importance for these protocols, a significant amount of risk relates to confidentiality protection (i.e. of undocumented or pregnant workers). Consultation from a person knowledgeable about worker issues could help provide perspective from the worker's perspective. Dr. Fisher noted that in the report and SAP discussions, it was recommended that people representing the handlers were included as part of the risk-benefit discussion.

Dr. Lehman-McKeeman commented on issues related to development of a large database with scientific validity and rigor. She acknowledged that the Board did not have access to many of the protocols, but did have documentation on how the database will be useful to EPA. She questioned whether (and which) procedures would be employed to determine whether a protocol was performed in a way to give consistent and reliable data. Investigators developing these protocols will need a method for assessing that the work was executed in such a way as to yield sound data.

Dr. Fenske reviewed the Board's response to the HSRB charge questions regarding EPA's need for new research on occupational handler exposure. The Board agreed that new data would be useful for EPA's pesticide risk assessments for agricultural workers, and commended the FIFRA SAP for clearly defining the rationale for the collection of new data. The idea of a database is robust and a sound way to develop a scientific approach to exposure assessment. Regarding additional information needed by the HSRB to assess handler research in general or individual protocols, Dr. Fenske commented that the draft framework on recruitment could be used to broaden discussion to include all occupational exposure to pesticides. This would include existing research on agricultural exposure to pesticides. For example, the completed Agricultural Reentry Task Force (ARTF) study could be used to inform the HSRB discussion concerning the agricultural handlers exposure database.

Concerning the distinction between intentional versus observational exposure, Dr. Fenske suggested that the HSRB consider occupational pesticide exposure studies to be intentional exposure studies, unless shown otherwise. These studies call for enough interaction with subjects and changes in their activities to be considered intentional exposures in most cases. The Board also should discuss issues related to employer-employee relationships, rather than ceding this manner to individual IRBs. Incentives to participate are provided to employers (such as free pesticides), which could impact the employer-employee relationship concerning employee participation. More clarity also is needed on the consequences to a worker who opts not to participate; such a worker may not be able to participate in his normal work activities. The complexities of recruitment of agricultural workers (i.e., language barriers, comprehension of risk, and true informed consent) also must be considered. Comprehending risk will involve not only surmounting language barriers but also addressing cultural differences in comprehending risk and ideas of health. A program in "cultural competencies" could help ensure that an investigator understands and is understood by the subject population.

Dr. Fenske recommended that the Board have the opportunity to review material related to the ARTF, which was developed in response to EPA requests for exposure data on workers who entered fields after pesticide treatments. Data were needed for a number of different "scenarios" involving multiple combinations of pesticide type, crop type, and worker activities. Data collection was funded in part by registrants and EPA has used this database for risk assessment activities since approximately 1999. The studies providing data to this database are similar to those expected to provide data for the occupational handlers exposure database.

Dr. Fenske concluded that the HSRB accepted EPA's rationale for its need for new data. Additional materials needed include a separate and new "governing document" that is not a generic description of the planned activities; a clear and appropriate plan for handling data, including its statistical analysis; and an explanation of the uses to which the data will be applied. Dr. Fenske also requested that the HSRB receive any plans for additional validation studies to determine the extent to which dermal exposure measurements may underestimate true exposure; any plans to broaden participation of the scientific community and parties with a direct interest in the database, such as the labor community; and any plans to meet the requirements of 40 CFR Part 26, as recommended by the HSRB.

Drs. Brimijoin, Lebowitz, and Krishnan commended Dr. Fenske on his analysis. Dr. Krishnan took exception to the language regarding the Board's policy on the definition of intentional exposure, commenting that the statement over-reached suitable boundaries. Dr. Fisher replied that the Board should discuss this matter further at the June 2007 HSRB meeting. Dr. Krishnan continued that EPA's need for new data was made very clear. He added that EPA and others should provide responses to the Board's suggestions of strategies to address scientific concerns. Dr. Carriquiry noted that, concerning what to expect from an appropriate, well-executed exposure study, WHO recently published a report on studies to establish exposure to pesticide in food, which could guide these discussions.

Dr. Lebowitz described a workshop held by EPA's ORD National Health and Environmental Effects Research Laboratory (NHEERL) to assess a variety of exposure types. At this workshop, discussion concerning development of a distinction between intentional exposure versus observational versus intervention studies was held. WHO regional offices published materials on various types of exposure pertinent to this issue. Dr. Fish agreed that the Board should attempt to educate themselves on these various matters before the June 2007 HSRB meeting.

Dr. Fisher summarized information to consider at the June 2007 HSRB meeting as including strategies for addressing scientific and ethics concerns indicated in the June 2006 HSRB meeting report; discussion of helpful analytic plans or models from other agencies (such as WHO), particularly statistical analysis plans to ensure scientific validity; and addition of statisticians to planning procedures. She stated that the Board would like to be presented with an overall plan for research, but noted that despite the existence of such a plan, each site protocol will need to be evaluated for human subject protections. She commented that there appear to be two tiers to this issue, namely whether the model and general plan are scientifically and ethically valid and how the protocol will be implemented at each site, i.e., how issues such as compliance with data collection and entry will be managed, subject safety, and monitoring of recruitment.

She also recommended reviewing the information from EPA's ORD NHEERL as suggested by Dr. Lebowitz, and discussing potential plans for community representation.

EPA's Need for New Research on Occupational Handler Exposure

Dr. Fisher presented the charge questions addressing EPA's need for new research on occupational handler exposure. She noted the Board's consensus that EPA's case for the need for new research was well made, based in part on the written material provided at this week's meeting.

Background

Mr. Jordan provided an overview of presentations related to EPA's pesticide handler exposure research programs. He described how EPA would use the data generated by the occupational exposure protocols.

EPA evaluates pesticides under the authority of FIFRA. For a pesticide to be registered, which is required before sale, EPA must determine that its use will not cause "unreasonable adverse effects" when used as directed. EPA must balance risks and benefits as part of the registration process. A wide range of potential risks are considered, including those to people who mix, load, or apply pesticides, i.e., handlers. To evaluate handler risks, EPA compares toxicity information with exposure information to determine the MOE, which is calculated by dividing the toxicity endpoint by exposure. Thus, a smaller MOE indicates increased risk. If the MOE does not meet EPA standards for registration, the sponsor could be asked to change the formulation of the pesticide or how it is handled, or to require the use of protective equipment. If these conditions fail to reduce risks associated with use of the pesticide, EPA can prohibit its use.

Data gathered as part of the Pesticide Handler Exposure Research Programs will be used to refine and improve EPA's ability to assess exposure. The research conducted under these programs will measure handler exposures for different use scenarios; assess the extent to which handler exposure is proportional to the amount of pesticide active ingredient handled; and characterize the distribution of unit exposures across handlers.

At present, EPA assumes a linear relationship between exposure and risk. Data gathered through handler exposure research will help to confirm this, or will provide evidence that the assumption is faulty. EPA has attempted to address this issue in the past. At the January 2007 SAP meeting, EPA requested advice on scientific issues affecting this and has been working to translate SAP advice into concrete decisions affecting how the advice can be effectively implemented in the design of research protocols. EPA also is cognizant of WHO protocols for assessing exposure. Mr. Jordan suggested that at the June 2007 HSRB meeting, it may be useful for the Board to delve more deeply into aspects of protocol design before addressing specific protocols. This depends on the ability of members of the AHTF and AEATF, along with other regulatory agencies, to use the general guidelines from the SAP report to generate concrete protocols.

Mr. Jordan clarified the distinction between observational research and intentional exposure research, as discussed previously by the HSRB. The draft language in regulations for research involving exposure of human subjects states that intentional exposure research encompasses the study of a substance in which exposure experienced by a human would not have occurred except by participation in the study. EPA decides which studies fall under these regulations and which do not. For example, worker re-entry studies would be considered intentional exposure research. The Board has not reviewed many such studies because most of the intentional exposure studies in the EPA database do not involve intentional exposure to toxicity and occurred before the new regulation regarding human subject protection went into effect. EPA is only required to bring older studies to the HSRB for review if the studies were conducted to identify or quantifying a toxic effect. The re-entry studies were not performed for this purpose, and thus were reviewed for ethics only within EPA.

Mr. Jordan concluded by offering to answer any Board questions about EPA's need for new data. If the HSRB approves, EPA will work with the task forces and other regulatory partners to design the best possible studies to evaluate pesticide handler exposure.

Board Discussion

Dr. Fisher asked whether the data from the ARTF studies had any relationship to the agricultural handler exposure data that will be collected. Mr. Jordan answered that both concern risks that may arise from pesticide use. He explained that EPA recognized two categories of occupational exposure. The first applies to handlers who mix, load, and apply pesticides. The second applies to those who are exposed to pesticides when they engage in work activities that bring them into contact with the pesticides. There are similarities in the methods used to assess worker exposure after re-entry and handler exposure, but the two assessments are not equivalent. Mr. Carley described examples of these similarities. Both studies use whole-body dosimetry rather than biomonitoring; ethics concerns about heat-related illnesses apply to both studies. Differences between the studies include the likelihood that language issues will be a larger concern for the re-entry studies than the handler studies. Third-party involvement in recruitment also is likely to be different, because re-entry workers are more likely to be hired as a crew, whereas handlers are more likely to be considered independent employees (such as members of an agricultural flying service). Different sets of best practices regarding recruitment will be needed for the two groups.

Dr. Fisher inquired if the HSRB would have the opportunity to discuss a statistical analysis plan, and whether the Board would receive background information on alternatives to such plans to prepare for review of specific protocols. Mr. Jordan responded that EPA would attempt to provide this information. Dr. Fisher noted that, for agenda planning, the Board would like to have an opportunity in June to discuss analytic approaches before reviewing protocols in October. Dr. Fenske commented that the ARTF studies address similar issues. He expressed concern that because the measurement methods are similar for the re-entry and handler exposure studies, the lessons learned are of interest more to EPA than the HSRB. EPA has a large database consisting of individual worker monitoring units and multiple scenarios (i.e., crop type, pesticide activity, etc.). There are a finite number of monitoring units and statistical analysis is being performed for this research because EPA is using the data to assess exposure. Given that

this database was complete in 2001 and given the demonstrated utility of the database, Dr. Fenske suggested that it may be instructive for the HSRB to hear from a member of the task force or EPA how the worker re-entry data are used. Mr. Jordan responded that EPA needs a better understanding of the relevance of the re-entry questions for preparation for review of the agricultural handler exposure protocols. With respect to Dr. Fenske's interest in the re-entry database, because it is a large database, EPA has not reviewed all the data or determined the statistical treatment of it. EPA has decided to discuss with the SAP issues for database use and incorporation of the data into a risk assessment database. This will take place during 2008. Depending on the HSRB agenda, coordination of this discussion with HSRB activity could be an option.

Dr. Carriquiry requested clarification of the relevance of the ARTF studies to the agricultural handler exposure studies and how review of the re-entry studies would help the HSRB assess the handler studies. Dr. Menikoff inquired whether there was a standard in the re-entry studies regarding how these new protocols handled subject protection if the studies required a change in pesticide use, or if these studies were more observational in nature. Mr. Carley explained that he and members of his team have reviewed all the studies in the re-entry and other databases, or sets of exposure studies, involving human subjects between February 2006 and six months later. These were all pre-rule studies, thus the distinction between intentional exposure and observational is less important. He considered his experience working with the ARTF and other task forces to be similar to that of his work with the AHETF. Both task forces encompass research to meet the needs of EPA and require sound, well-executed protocols. Similar to other pre-rule studies, these vary widely in the completeness of ethics reporting. The standard used for ethics review was to require clear and convincing evidence that the study was intentionally or seriously deficient and ensure that neither children nor pregnant or nursing women were involved as subjects. Based on information available in the archive, these studies were not reviewed as intensely as current studies.

Dr. Menikoff questioned whether information from the ARTF studies could inform review or development of the AHETF studies. Mr. Carley explained that the activities of re-entrant workers and handlers are different. In addition, the change in the rule regarding human subject protection will have a significant impact. Dr. Fenske clarified that he was not asking the HSRB to review the ARTF studies. His intention was to determine if information useful for review of the AHETF studies could be garnered from the existing ARTF database. His major concern is that a statistical plan is not in place for the AHETF study, despite the fact that this study is already underway. If a statistical plan for ARTF exists, it could be shared with the HSRB because these studies also involve monitoring activities similar to those in the professional handler scenarios. Dr. Fisher noted that because the ARTF work was performed pre-rule, issues concerning human subject protection will not be relevant. A statistical plan would be relevant to the HSRB only if it is equivalent to what will be used for AHETF protocols. She stated that it is EPA's role to determine the relevance of ARTF to AHETF.

Dr. Carriquiry questioned whether the Board will receive background material when they review the handler exposure protocols. She noted that the AHETF proposed a set of guidelines that the SAP reviewed and critiqued, but was uncertain if an agreement was reached on some important study aspects, such as collecting repeated observations on the same person, random

versus systematic sampling of scenarios (termed factor sets for AHETF), and the appropriate number and levels of factor sets. She inquired if any consensus had been achieved on these items. Dr. Carriquiry also asked under which guidelines the protocols had been written. Mr. Jordan said that the SAP has offered advice that could be characterized as asking EPA to consider these issues, but did not provide definitive answers. He added that he had only recently received the SAP report. EPA has been considering these issues and making progress internally, but does not currently have answers to these questions. Conversations among EPA and AHETF personnel will lead to development of a statistical design for the study that will address these issues. There must be consideration of matters, such as the quality of the scientific information and its applicability, cost, level of understanding, how to choose the most important factors, and EPA's intended use of the information that must be balanced in the development of specific protocols.

Drs. Brimijoin, Carriquiry, and Chambers reviewed the HSRB's response to whether EPA had justified that additional data were needed. Dr. Chambers agreed with EPA's need for additional data. Dr. Brimijoin also agreed, and commented that in June 2006 HSRB meeting he heard EPA's elaborate plans for collecting large amounts of data, but a sense of how that data would be analyzed was lacking; EPA should have a plan in place for analyzing the data before data collection begins. Dr. Carriquiry added that EPA should be aware of the expertise of the HSRB members who could help review such a plan.

Dr. Fisher asked Drs. Hoel and Zhu for comments on EPA's justification for its need for additional handler exposure data. Dr. Hoel opened by asking whether the data would have a significant impact on setting standard. He stated that he was unconvinced that, given the human exposure involved in these studies, the data could not be obtained through observational studies. He commented that for toxic substances, information on pharmacokinetics and genetic variability of the exposed population is needed. He found the idea of intentional exposure of human subjects to toxic substances troubling. Dr. Fisher explained that the products used in these studies are already in use. The goal of the handler exposure research is to determine handlers' exposure levels that occur during the course of their normal work activities. In this case, "intentional" refers to the nature of the control. The pesticides are the same as or similar to those the workers ordinarily use. The workers will not be exposed to any level or quality of pesticide to which they would not ordinarily be exposed. Dr. Zhu noted that a controlled exposure study would be more definitive than an occupational exposure study.

EPA FIFRA SAP January 2007 Review and Report: Worker Exposure Methods

Background

Dr. Steven Heeringa introduced himself as the FIFRA SAP Chair. Dr. Heeringa, a statistician at the University of Michigan, is an expert in statistical design and analysis for population-based research. He acknowledged Dr. William Popendorf of Utah State University, who also serves on the FIFRA SAP. Dr. Popendorf introduced himself as a professor of industrial hygiene at Utah State University who has conducted exposure studies for approximately 30 years. Dr. Heeringa stated that he would outline the FIFRA SAP report and describe the main topics. The SAP operates as an advisory panel under FACA. SAP deliberative sessions involve review of advance material by a permanent panel of seven members and an ad hoc set of 10 to 12 other specialists. The deliberations of the SAP are public and information included in the SAP report must have been discussed openly at the public meeting.

Dr. Heeringa began review of the FIFRA SAP report by stating that the SAP supported EPA's assessment of the limitations of existing pesticide handler exposure data. The panel identified eight limitations: 1) inadequate QA/quality control documentation; 2) high levels of measurement uncertainty due to the methodology used; 3) large amounts of censored (undetectable) data; 4) incomplete dermal sampling data; 5) high levels of observation clustering with unknown intra-class correlation; 6) data based on short sampling periods, creating difficulties with extrapolating to full day exposures; 7) many scenarios with too little data; and 8) scenarios that do not reflect modern work practices and technologies.

The SAP judged the AHETF plan to be reasonable, with some critiques. The monitoring duration criteria were considered too stringent to capture real-world, short-term use scenarios. The biomonitoring data criteria were deemed too restrictive because they did not allow for extrapolation to humans from rat or pig. The air sampling criteria needed to be refined and dermal sampling criteria improved.

Dr. Heeringa explained that the SAP recommended whole body passive dosimetry because it would provide minimum uncertainty and maximum protections (by minimizing skin exposure). Patch dosimeters are subject to uncertainty because of the need to extrapolate to the whole body surface. Biomonitoring was permitted, but not required in the protocols. The primary use of biomonitoring was considered to be as an indication of whole body dosimeter breakthrough, but occurrence of a small breakthrough would not require data to be discarded and was not required for acceptance of dosimeter results. Hand rinsing was considered as a way to evaluate hand exposure. Hand rinsing methods were recommended over wiping (which may underestimate exposure), but this method carries uncertainty because of the effect of rate of adsorption on recovery efficiency. Field conditions also may confound these measurements, because participants might rinse their hands more or less frequently than anticipated. The SAP agreed that a passive dosimetry approach was sufficient to support EPA's data needs and can generate data that can be used to develop acceptably predictive estimates of worker exposure for a wide variety of scenarios and worker activities.

Dr. Heeringa explained that the SAP considered the issues surrounding the assumption of linearity of exposure to be a statistical issue. Model assumptions were built into the AHETF proposal, including that of a linear relationship between exposure and active ingredient handled. Sample design decisions will depend on this linear assumption. If the assumption holds, statistical plans can be streamlined. If this relationship is found not to be linear, it will be more difficult to develop these plans. AHETF plans to measure covariates that are not currently included in the pesticide handler exposure database, such as temperature, humidity, and certain behaviors, that might be used to better model the relationship between exposure and active ingredient handling. The SAP recommended additional research concerning the potential role of these other covariates in modeling exposure.

The SAP also considered the issue of repeated measurements. A majority of the SAP members recommended de-emphasizing within-worker variability (repeated measures) and using resources to add clusters (i.e., sites, days, or locations) and increase sample size to improve precision. A minority of members recommended repeated measures to capture measures of intra-class correlation. This approach would provide better information concerning the relationship between repeated measures and biomonitoring to help understand the results of biomonitoring relative to exposure. For the database itself, the SAP recommended spending funds on individual worker observations over repeat observations of an individual worker.

The SAP also responded to statistical questions concerning sample size and allocation. In general, the SAP accepted AHETF recommendations concerning the cost of the studies. Most studies would cost in the range of hundreds of thousands of dollars. The applicability of the linear model is a critical assumption, because sample size and allocation recommendations in the AHETF report were based on this model. AHETF and EPA will need to discuss precision requirements, because EPA ultimately must judge whether the data meet fundamental precision requirements for their use in regulatory activities. A range of a factor of three was placed on the geometric mean for the 95 percent CI; EPA would tolerate an estimate that was acceptable within a threefold increase over the geometric mean or a one-third decrease under the geometric mean, essentially a nine-fold range in the predicted unit exposure.

EPA originally recommended minimum studies consisting of approximately 1,500 workers each to populate the initial database. The SAP encouraged EPA to use larger numbers of clusters. Dr. Heeringa commented that in his research, 500 clusters is typical, but five clusters, as determined by EPA, may be sufficient given the model assuming linearity between exposure and active ingredient and the level of precision that can be tolerated for risk assessment activities; small studies of five clusters and five workers may be an adequate starting point. The SAP noted, however, that the acceptance of small sample sizes depends heavily on the assumptions made in the statistical design. The SAP also was concerned with the proposed purpose of the nature of sample selection and the dependency on the linear model. The SAP discussed the potential for bias and offered an alternative stratified approach, but understood that the high costs of worker exposure measurements constrain sample design options.

Dr. Heeringa summarized SAP's findings by stating that the Panel supported EPA's position on the need for updated standardized exposure data to replace or supplement existing data, supported passive dosimetry with a preference for whole body dosimeters, recognized the

large uncertainties inherent in measuring worker exposures, and had concerns about the exposure model and sample selection.

Dr. Carriquiry opened discussion by stating that she believed the SAP report was incorrect regarding the issue of repeated measurements. If the objective of the data is to determine an estimate of the range of typical exposures, failing to collect replicate data on a subject of workers would result in a biased estimate. The mean and median would be correct, but the range would be too large. Some replicate observations are needed to remove within-worker variability. For EPA, the estimates at either end of the range of exposures may be significantly over-estimated if this step is not performed. Dr. Heeringa explained that the SAP recommended 15 to 20 observations, but repeat measures did not need to be a part of each study. The report does note the need to capture repeat observations in some studies. Dr. Carriquiry added that although within-worker variance would not always be the same, an estimate from one study could be used to adjust the data from other studies that may have only one observation per worker. Dr. Heeringa remarked that the SAP believed that repeat observations should be relevant to actual practices. For example, if a pesticide is applied every 2 weeks, repeat measurements should be performed every 2 weeks. Dr. Popendorf added that this also is relevant to sample and pesticide selection, because workers should not be forced to use the same pesticide twice (or only twice).

Dr. Lebowitz expressed his appreciation for the review of the SAP report, particularly the review of different methods and comparison of passive dosimetry to biomonitoring, and commented on the report's discussion of issues of biomonitoring exposure related to the possibility of other substances giving rise to the same metabolites as the monitored pesticides. He agreed with the discussion of the importance of measuring within-worker variability, particularly the recognition that in certain settings this activity is more important than in others. Dr. Lebowitz addressed the issue of costs by suggesting that extending the time over which observations occur could address the need to satisfy both sample size and measurement replicates. He considered that exposure dose calculations needed to be assessed, particularly in terms of how the data will be used in risk assessment, and the issue of aggregate and cumulative exposure. He commended the SAP on its discussion of covariates, effect modifiers, and confounders.

Dr. Lebowitz asked Drs. Heeringa and Popendorf to comment further on the importance of biomonitoring. Dr. Popendorf responded that the SAP considered the tradeoffs between biomonitoring and dosimetry. Using passive dosimetry meant that the back calculations performed by using exposure data to drive recommendations results in the least amount of uncertainty for EPA. Dr. Heeringa added that during the meeting, the issue of biomonitoring was discussed in the context as a necessary step to measure exposure, not necessarily dose. The SAP understood the next steps beyond determining dose would include determining dose at target organs and subsequent biological processes. For certain well-understood compounds with established clearance rates, biomonitoring can be useful, but to assess the distribution of exposures in the population by back-calculating from the presence of a pesticide metabolite in urine back to skin exposures was considered less optimal. Dr. Chambers agreed, adding that there was insufficient pharmacokinetic information on most pesticides to perform back-calculations from presence in urine to skin exposures. Dr. Heeringa continued that passive

dosimetry data could be compared to biomonitoring results for some well-characterized substances, but the panel believed that the data would be similar enough to warrant passive dosimetry.

Dr. Krishnan commented that reverse calculations can be performed if physiology-based kinetic models are available. He also noted that he believed the inability to extrapolate from rat data to interpret biomonitoring data may be too restrictive. If the permeability constant or coefficient from rat studies is used, exposure concentrations could be underestimated by a factor of approximately 10. Unless there is evidence that the permeability for a particular pesticide is similar in rats and humans, reconstructing based on biomonitoring data using rat pharmacokinetics is acceptable; if not, this would introduce greater uncertainty. In these cases, equating the metabolite or pesticide present in urine to the absorbed dose is acceptable.

Dr. Krishnan continued by asking if collection of biomonitoring data would help address the effectiveness of the dosimetry monitoring. Dr. Heeringa replied that the SAP recommended that some biomonitoring data be collected to detect breakthrough on the whole body dosimetry. The SAP did not, however, recommend that all observations include biomonitoring as a method for quality control. Biomonitoring data could be used to develop qualitative and quantitative parameters, or in calibration studies. Dr. Chambers added that the SAP was not enthusiastic about biomonitoring because many of the metabolites of the pesticides are scarce or have long half-lives. Dr. Heeringa agreed, adding that the SAP did not want to require that observations be excluded from the database because biomonitoring indicated breakthrough occurred; also, the SAP did not want workers to be excluded if they declined to participate in urine testing. Dr. Fisher summarized that the SAP was not highly enthusiastic about including biomonitoring because the major metabolites for many pesticides were only a small portion of metabolites, and long half-lives would require extensive urine collections with likely poorer compliance of participants.

Dr. Fisher asked Dr. Heeringa to comment on the lack of information on the workers themselves or their work activities, and what sort of data would be needed to develop a design that accounts for the expected variability. Dr. Heeringa explained that there were two dimensions to this question. First, EPA and the registrant's agriculture experts understand many of the practices workers use for applying pesticides. This is important for understanding factors critical to exposure, and understanding these factors will help design the study. However, although the practices are known, their frequency and distribution, across individuals in space and time, is not well known. Exposure can be different depending on variables such as site and crops grown. This information would be used in the design to determine sample allocation. The goal of the protocols is to maximize procedures or measures that have high variability of exposure, but it is unknown how many workers these practices affect. Dr. Fisher questioned if much of the information gathered would be product- or context-specific. She inquired about the nature of the data in terms of specificity versus breadth, what elements would be most useful, and the dangers of over-generalization of data to specific product context. Dr. Popendorf explained that the database will be generic, not product-specific. Data would be categorized by use scenarios, which currently are being defined. The chemicals used were selected on the basis of available methods to detect these chemicals at low levels. Exposure information should be broadly applicable to the products used in that setting and for that formulation. Dr. Popendorf

continued that in terms of sample allocation, a stratified approach in terms of a given exposure or handling amount could be used to predict exposures to the population. Dr. Heeringa commented that the AHETF plan defined a restricted set of scenarios, formulations, and activity types. These were considered to be realistic starting points, and eventually subactivities could be determined and differentiated.

Dr. Fenske commented that the Board had concerns when it reviewed some of the AHETF protocols in June 2006. For example, a protocol was designed to have 10 people in one scenario involving open loading of liquid in an air-blast application. Within that scenario, one person may have used five containers containing 5 gallons each, while another person may have used one 25-gallon container. Other conditions, such as wind speed, also could affect exposure. The HSRB had the sense that there was a high degree of variability within a scenario, and it was not clear if within-scenario variations in the size of the containers used, frequency of opening the containers, and so forth, were included to create a range of values or to use as a variable in statistical analysis. Dr. Fenske questioned whether the study had sufficient power to use these variables in an analysis. Dr. Heeringa responded that study design is under the purview of EPA, but the SAP considered this. The SAP considered whether the experiments should be structured with control variables, but given the many behavioral and other variables involved, it is not possible to control for all sources of variability. The goal is to capture data on the covariates, although it will not be possible to statistically control for their presence. It was deemed important to capture this data so database users could have an idea of the variability involved and know how the data were captured.

Dr. Lebowitz questioned if there was sufficient discussion at the SAP meeting about the quality and acceptability of existing data in the pesticide handler exposure database for certain factor sets that would allow dose data to be used. He added that air monitoring might be important in certain settings and contribute to total dose. He asked whether the SAP had discussed measuring ingestion through food or water contamination and how these exposure pathways might contribute to estimates of exposure. Dr. Popendorf explained that there was little discussion of secondary exposures. These measurements could be more applicable to biomonitoring experiments. Most existing data demonstrate that excretion and dermal monitoring appear to correlate well numerically; in general, oral ingestion is not considered an important component of exposure. Dr. Chambers agreed, and noted that ingestion data could confound biomonitoring results. Dr. Heeringa added that the SAP did not discuss incidental contamination at length, which was judged to be small. Including hand rinsing as part of some protocols may help assess this.

Dr. Heeringa continued that the SAP did not consider the data in the existing pesticide handler exposure database to be obsolete for risk assessment. If qualified studies exist in the database (i.e., observations on techniques and scenarios currently in use by pesticide handlers), this data could be used for current risk assessment activities. However, the SAP made no recommendations concerning the incorporation of this data into the new database.

Dr. Sharp commented on medical monitoring issues, including the absence of the involvement of occupational health physicians in these protocols. He questioned if the SAP had considered recommending inclusion of such professionals to help determine actions to take if a

level of exposure is identified that should trigger medical assessment. Dr. Heeringa stated that the SAP discussed health concerns, such as heat and duration of exposure to heat. Dr. Chambers added that the SAP is asked to review scientific issues, not health issues. Dr. Fisher asked whether SAP thought data that already has been collected, could be used, implications for models and procedures, and whether it could provide pilot information for the design of this study. Dr. Chambers added that the quality of the existing data has been graded, and she believed that high quality data would be used.

Dr. Fisher asked if drop-outs or partial data were anticipated and whether there was advice for using (or eliminating) such data. She questioned if these issues were considered in discussion of study design and sample size and selection. Dr. Heeringa explained that the SAP did not discuss drop-out issues at length, but did discuss length of observation. The protocols in question cannot strictly control the length of time taken to apply materials, thus, the task force developed targets for exposure periods to reflect normal work activities. These values would be normalized. The SAP did not discuss individual drop-outs, but concluded that the protocols should reflect typical work day activities.

Dr. Zhu commented that he felt strongly that pharmacokinetic-pharmacodynamic data should be used to reduce uncertainty. Occupational exposures should be high enough for biomonitoring. He did not believe there was good evidence that biomonitoring would be unsuccessful in this setting, and that, in the future, investigators would regret that such data were not collected. Biomonitoring data are useful because it can provide the physiological link to the next processes occurring after exposure and will help estimate total and cumulative exposures. If a physiologically based modeling approach is desired, repeat measurements are needed to provide reliable physiology data, and will help ensure the data are useful in the future. Dr. Zhu stated that he was troubled by the sample sizes described for this research. Exposure is likely to be linear, but sample size determination is based solely on this assumption of linearity, and perhaps does not provide the best basis for sample or cluster size estimation. He added that collecting covariates (such as use and application methods) is useful, but standards are required for collection of those data.

Dr. Heeringa explained that these data will be used for evaluation in the context of a general database that has information on a distribution of exposures. The arguments for biomonitoring and repeated measurements are valid; however, most biomonitoring and physiological models are not appropriate for these settings. These are tier 1 or 2 screening studies to determine if a significant risk exists. Dr. Heeringa agreed that if the interest was in developing physiological models, repeated measurements were needed; however, measurements for such modeling activities are more properly made under controlled laboratory conditions, rather than in the field. Dr. Chambers added that pharmacokinetic-pharmacodynamic models are available only for a small number of compounds and may not apply to all the compounds being measured. Dose applies to all compounds. Dr. Brimijoin noted that if passive dosimetry is performed in a reliable manner to monitor exposure, biomonitoring can only be considered a supplemental tool that will provide little information on absorption; if the dosimetry garments function properly, most pesticide absorption/uptake will be blocked. Dr. Brimijoin agreed with Dr. Heeringa concerning the issue of developing pharmacokinetic-pharmacodynamic models; collecting biomonitoring data for this is a sound idea, but should be performed in a different

setting. Dr. Fenske stated that biomonitoring is important, but the protocols reviewed in June 2006 called only for passive dosimetry. The task force chose specific compounds based on their low toxicity, and good pharmacokinetic-pharmacodynamic models may not be available for many of these. The goal of this work is to collect good quality exposure data across a number of scenarios for risk assessment activities. Validation of hand washing, face washing, biomonitoring, or other exposure assessment techniques should be considered side studies.

Dr. Popendorf clarified questions concerning sample size. He stated that the design the SAP was shown estimated that five people in five clusters for a given scenario was reasonable to achieve a precision factor of 3. A secondary goal of these analyses was to detect linearity. If linearity is not shown, it is true that data collected on potential covariates likely will not help determine which covariates correlate with variability. The SAP suggested, that, as a backup to the linearity assumption, some other hypotheses be developed in terms of the major potential drivers for exposure in a given scenario and use the covariate as a potential way to validate and use data in a regulatory process. He summarized that precision and linearity were the major drivers for sample size determination. Dr. Heeringa added that the SAP understood that, if the linearity assumption does not hold, increased sample size will be needed to retain the same level of precision. The SAP's recommendation for this is to increase the number of clusters. The Panel also recommended that assumptions be revisited as data are gathered.

Dr. Brimijoin commented that in the statistical treatment of data, the focus would be on multiple clusters with multiple individuals involving a particular mode of application, regardless of the type of compound, or also stratified by compound. He stated that when he first saw the AHETF protocols, he did not think the protocols included sufficient replicates to be of use. He asked whether data would be consolidated by putting together information from different compounds, but that had the same amount (milligrams) of active ingredient. Dr. Fisher summarized that a difficulty in review of this work seemed to be how to understand that there is a great deal of information that cannot be specific. The data are needed, and there is no way to have a sample size large enough to answer exposure questions for every ingredient, timeframe of exposure, or application method. A rationale is needed to determine which covariates are most important. Other questions concern the validity of the assumption of a linear model and how the data can be used, given this lack of specificity, the variability of ingredients, etc., to support risk assessment activities. Dr. Chambers stated that the assumption is that the handling activity and formulation will determine exposure. The identity of the pesticide measured is less important; if two pesticides have the same formulation and are handled in the same amounts and in relatively the same manner, exposure will be similar. These protocols are intended only to measure dose, not toxicity equivalents. Dr. Popendorf agreed, noting that the data would be used only to assess exposure; absorption and toxic effect would be chemical-specific. Different formulations, i.e., liquid or powder, will be measured separately.

Public Comments

Dr. Fisher invited oral public comment on the EPA FIFRA SAP January 2007 Report on Worker Exposure Methods. No oral public comments were received.

Board Discussion

Dr. Fisher asked Board members to respond to the question concerning additional information needed for review of handler research in general or individual protocols. Dr. Fenske began, stating that the Board needs information from EPA concerning the use of information in the re-entry workers database, which has parallels to AHETF, for risk assessment activities. He also requested clarification of the definition of "intentional exposure" versus "observational" research. He recommended consideration of the term "scripted" instead of "intentional exposure," because the exposure is not "intentional" but is staged or modified to meet the practical considerations of obtaining useful data. The HSRB should discuss this with EPA. Dr. Fenske added that Mr. Jordan had indicated that discussions on these terms were in progress at EPA, and perhaps could share any relevant information concerning these matters. Dr. Fenske related other information requests, including a governing document, such as that submitted to the SAP, or the joint document from EPA, California EPA, and Health Canada, which aptly justified and explained data needs. He also requested feedback on stated EPA plans for additional validation studies to determine whether dermal exposure measurements underestimate true exposure; broaden participation of the scientific community and parties with direct interest, such as the labor community; and plans for meeting the requirements of 40 CFR Part 26.

Dr. Lebowitz observed that his points had been expressed in the SAP discussion, which also clarified many of his questions. Concerning additional information, Dr. Lebowitz stated that the Board did not yet have a clear understanding of the study designs that would be employed and final decisions regarding sample size, analyses, and handling biases. As a general recommendation, he suggested that the AHETF attempt to save time and money by including appropriate studies in the existing pesticide handlers exposure database in its own database. He added that he will be interested in seeing how the revised protocols address issues, such as standardization of exposure monitoring, and other subjects raised by the SAP.

Dr. Lehman-McKeeman stated that additional information was needed to clarify how recognized covariates would be handled and integrated into data analyses and how this would affect study design. She also asked for identification of the study director regarding who would approve a study or oversee the execution of the studies.

Dr. Menikoff requested more discussion of how pesticides are chosen for studies and how that changes conditions for workers. He stated that "intentional" exposure means exposure to a substance that would not otherwise occur. He inquired whether ethical justification was needed to alter the pesticide used, and whether investigators could instead locate a setting in which the desired pesticide already was in use; this would help eliminate some ethical issues.

Dr. Chambers disagreed with comments on the definition of intentional exposure. In her opinion, EPA's analysis of this issue should be heard before the Board develops its own definition. Dr. Fenske agreed, adding that it is not the HSRB's role to develop the definition, but to provide advice. He commented to Dr. Menikoff that, in his understanding, the AHETF always attempts to find conditions that do not have to be altered for research purposes, but this is limited by the availability of analytical capabilities for a given compound. Appropriate substitutes must sometimes be suggested. Dr. Fenske also addressed the issue of heat related illnesses. The

procedure for collecting data places workers at risk for heat stress; Dr. Fenske asked Dr. Menikoff if this was related to the idea of changing working conditions. Use of the dosimeter garments may decrease pesticide exposure, but increase another type of hazard. Dr. Menikoff responded that this did meet his idea of changing conditions. He added that he was not debating whether the research fit within the applicable statutes. His recollection was that in many cases, the investigators supplied the pesticide. If this is the case, the investigators must justify why they cannot find a location at which that pesticide already is in use. Dr. Fisher cautioned against assuming that use of a different pesticide increases risk.

Dr. Fisher summarized the HSRB informational needs. A plan similar to that provided to the SAP is needed, not for critique, but to further understanding of the AHETF. Information also is needed concerning how EPA will evaluate its linear model assumption, given the SAP's recommendations about evaluating this model during the data collection process and identifying an alternate approach, if necessary. The HSRB members also asked for information concerning how sample size would be determined; strategies for replacement of missing or partial data; a statistical analysis plan; identification of covariates to be collected and a rationale for emphasis on some covariates versus others; assessment of the need for a subset of repeated measurements to control for some variability; identification of the type of biomonitoring data that would be collected as a check for passive dosimetry; information concerning validation of data collection, entry, training at the site, and identification of relevant IRBs; information on whether passive dosimetry over- or under-estimates dosage and whether statistical analyses or biomonitoring data will help determine if a bias exists; information on sampling frame and where to focus data collection, based on usage patterns for products; and a rationale for the use of pesticides at each site if they differ from those normally used, to inform ethics discussions on toxicity and side effects.

Dr. Lewis thanked the Board members for their work and EPA for preparing the meeting. He stated that the next HSRB meeting is tentatively scheduled for June 27-29, 2007.

Dr. Fisher adjourned the meeting.

Respectfully submitted:

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

Certified to be true by:

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

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

Attachments

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

Attachment A

EPA HUMAN STUDIES REVIEW BOARD MEMBERS

Chair

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

Vice Chair

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

Members

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

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

Gary L. Chadwick, PharmD, MPH, CIP
Associate Provost
Director, Office for Human Subjects Protection
University of Rochester
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Janice Chambers, Ph.D., D.A.B.T.
William L. Giles Distinguished Professor
Director, Center for Environmental Health Sciences
College of Veterinary Medicine
Mississippi State University
Mississippi State, MS

Richard Fenske, Ph.D., MPH
Professor
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University of Washington
Seattle, WA

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Co-Director, MA in Clinical Investigation
Boston University School of Medicine
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Tucson, AZ

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

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

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

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

* Not in attendance

Attachment B
Federal Register Notice Announcing Meeting

Human Studies Review Board; Notice of Public Meeting

[Federal Register: March 26, 2007 (Volume 72, Number 57)]
[Notices]
[Page 14101-14103]
From the Federal Register Online via GPO Access [wais.access.gpo.gov]
[DOCID:E7-5492]

ENVIRONMENTAL PROTECTION AGENCY
[EPA-HQ-ORD-2007-0216; FRL-8291-4]

Human Studies Review Board; Notice of Public Meeting

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

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

DATES: The public meeting will be held on April 18, 2007 from 10 a.m. to approximately 5:30 p.m., Eastern Time and April 19-20, 2007 from 8:30 a.m. to approximately 5:30 p.m., Eastern Time.
LOCATION: Environmental Protection Agency, Conference Center—Lobby Level, One Potomac Yard (South Bldg.), 2777 S. Crystal Drive, Arlington, VA 22202.
MEETING ACCESS: Seating at the meeting will be on a first-come basis. To request accommodation of a disability please contact the person listed under FOR FURTHER INFORMATION CONTACT at least 10 business days prior to the meeting, to allow EPA as much time as possible to process your request.
PROCEDURES FOR PROVIDING PUBLIC INPUT: Interested members of the public may submit relevant written or oral comments for the HSRB to consider during the advisory process. Additional information concerning submission of relevant written or oral comments is provided in Unit I.D. of this notice.

FOR FURTHER INFORMATION CONTACT: Any member of the public who wishes further information should contact Paul Lewis, EPA, Office of the Science Advisor, (8105R), Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460; telephone number: (202) 564-8381; fax: (202) 564 2070; e-mail address: lewis.paul@epa.gov. General information concerning the EPA HSRB can be found on the EPA Web site at http://www.epa.gov/osa/hsrb/.
ADDRESSES: Submit your written comments, identified by Docket ID No. EPA-HQ-ORD-2007-0216, by one of the following methods:

- Internet: http://www.regulations.gov: Follow the on-line instructions for submitting comments.
- E-mail: ORD.Docket@epa.gov.
- Mail: Environmental Protection Agency, EPA Docket Center (EPA/DC),

ORD Docket, Mailcode: 28221T, 1200 Pennsylvania Ave., NW, Washington, DC 20460.

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

Instructions: Direct your comments to Docket ID No. EPA-HQ-ORD-2007-0216. EPA's policy is that all comments received will be included in the public docket without change and may be made available online at http://www.regulations.gov, including any personal information provided, unless the comment includes information claimed to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Do not submit information that you consider to be CBI or otherwise protected through http://www.regulations.gov or e-mail. The http://www.regulations.gov Web site is an “anonymous access” system, which means EPA will not know your identity or contact information unless you provide it in the body of your comment. If you send an e-mail comment directly to EPA, without going through http://www.regulations.gov, your e-mail address will be automatically captured and included as part of the comment that is placed in the public docket and made available on the Internet. If you submit an electronic comment, EPA recommends that you include your name and other contact information in the body of your comment and with any disk or CD-ROM you submit. If EPA cannot read your comment due to technical difficulties and cannot contact you for clarification, EPA may not be able to consider your comment. Electronic files should avoid the use of special characters, any form of encryption, and be free of any defects or viruses.

SUPPLEMENTARY INFORMATION:

I. Public Meeting

A. Does this Action Apply to Me?

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

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

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

Docket: All documents in the docket are listed in the http://www.regulations.gov index. Although listed in the index, some information is not publicly available, e.g., CBI or other information whose disclosure is restricted by statute. Certain other material, such as copyrighted material, will be publicly available only in hard copy. Publicly available docket materials are available either electronically in http://www.regulations.gov or in hard copy at the ORD Docket, EPA/DC, Public Reading Room. The EPA/DC Public Reading Room is located in the EPA Headquarters Library, Room Number 3334 in the EPA West Building, located at 1301 Constitution Ave., NW, Washington DC. The hours of operation are 8:30 a.m. to 4:30 p.m. Eastern Standard Time, Monday through Friday, excluding Federal holidays. Please call (202) 566-1744 or e-mail the ORD Docket at ord.docket@epa.gov for instructions. Updates to Public Reading Room access are available on the Web site (http://www.epa.gov/epahome/dockets.htm).

EPA's position paper(s), charge/questions to the HSRB, and the meeting agenda will be available by late March 2007. In addition, the Agency may provide additional background documents as the materials become available. You may obtain electronic copies of these documents, and certain other related documents that might be available electronically, from the regulations.gov Web site and the HSRB Internet Home Page at http://www.epa.gov/osa/hsrb/. For questions on document availability or if you do not have access to the Internet, consult the person listed under FOR FURTHER INFORMATION CONTACT.

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

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

a. Explain your views as clearly as possible.

b. Describe any assumptions that you used.

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

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

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

D. How May I Participate in this Meeting?

You may participate in this meeting by following the instructions in this section. To ensure proper receipt by EPA, it is imperative that you identify docket ID number EPA-HQ-ORD-2007-0216 in the subject line on the first page of your request.

a. Oral comments. Requests to present oral comments will be accepted up to April 11, 2007. To the extent that time permits, interested persons who have not pre-registered may be permitted by the Chair of the HSRB to present oral comments at the meeting. Each individual or group wishing to make brief oral comments to the HSRB is strongly advised to submit their request (preferably via email) to the person listed under FOR FURTHER INFORMATION CONTACT no later than noon, Eastern Standard Time, April 11, 2007 in order to be included on the meeting agenda and to provide sufficient time for the HSRB Chair and HSRB Designated Federal Officer (DFO) to review the agenda to provide an appropriate public comment period. The request should identify the name of the individual making the presentation, the organization (if any) the individual will represent, and any requirements for audiovisual equipment

(e.g., overhead projector, LCD projector, chalkboard). Oral comments before the HSRB are limited to five minutes per individual or organization. Please note that this limit applies to the cumulative time used by all individuals appearing either as part of, or on behalf of an organization. While it is

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our intent to hear a full range of oral comments on the science and ethics issues under discussion, it is not our intent to permit organizations to expand these time limitations by having numerous individuals sign up separately to speak on their behalf. If additional time is available, there may be flexibility in time for public comments. Each speaker should bring 25 copies of his or her comments and presentation slides for distribution to the HSRB at the meeting.

b. Written comments. Although you may submit written comments at any time, for the HSRB to have the best opportunity to review and consider your comments as it deliberates on its report, you should submit your comments at least five business days prior to the beginning of the meeting. If you submit comments after this date, those comments will be provided to the Board members, but you should recognize that the Board members may not have adequate time to consider those comments prior to making a decision. Thus, if you plan to submit written comments, the Agency strongly encourages you to submit such comments no later than noon, Eastern Standard Time, April 11, 2007. You should submit your comments using the instructions in Unit I.C. of this notice. In addition, the Agency also requests that person(s) submitting comments directly to the docket also provide a copy of their comments to the person listed under FOR FURTHER INFORMATION CONTACT. There is no limit on the length of written comments for consideration by the HSRB.

E. Background

A. Topics for Discussion

The HSRB is a Federal advisory committee operating in accordance with the Federal Advisory Committee Act (FACA) 5 U.S.C. app.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: (a) Research proposals and protocols; (b) reports of completed research with human subjects; and (c) how to strengthen EPA's programs for protection of human subjects of research. The HSRB reports to the EPA Administrator through EPA's Science Advisor.

At the April 2007 meeting of the HSRB, EPA will present for HSRB review:

• The results of two completed insect repellent efficacy studies on an aerosol formulation of the active ingredient IR3535, studies which the Agency intends to rely in making registration decisions. Protocols for this research were reviewed by the Board at its June and October 2006 meetings.
A proposal for a new field study of the effectiveness of products containing oil of lemon eucalyptus in repelling mosquitoes.

• Completed studies of human skin irritation and skin sensitization on two pending pesticide products whose use would involve extensive dermal exposure. These studies were conducted before the effective date of EPA's human studies rules (April 7, 2006).

• EPA's assessment of the need for new research on the exposure received by occupational handlers who mix, load, or apply agricultural or antimicrobial pesticides.

• An EPA "draft framework" concerning best practices for recruiting and enrolling subjects in studies of occupational exposure.

In addition, at the Board's request, EPA will present its interpretation and application of the standard in 40 CFR 26.1705: "EPA shall not rely on data from any research initiated after April 7, 2006, unless EPA has adequate information to determine that the research was conducted in substantial compliance with [EPA's human studies rules]." Finally, the Board may also discuss planning for future HSRB meetings.

B. Meeting Minutes and Reports

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

Dated: March 19, 2007.

George M. Gray,

Science Advisor

[FR Doc. E7-5492 Filed 3-23-07; 8:45 am]

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Attachment C

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

APRIL 18-20, 2007*
ONE POTOMAC YARD
ARLINGTON, VA

HSRB Web Site: http://www.epa.gov/osa/hsrb/
Docket Telephone: (202) 566-1752
Docket Number: EPA-HQ-ORD-2007-0216

Wednesday, April 18, 2007

10:00 a.m. **Convene Meeting and Identification of Board Members**
Celia Fisher, Ph.D. (HSRB Chair)

10:15 a.m. **Welcome**
Warren Lux, MD (Human Subjects Research Review Official, Office of the Science Advisor, EPA)

10:25 a.m. **Opening Remarks**
Mr. Jim Jones (Principal Deputy Assistant Administrator, Office of Prevention, Pesticides, and Toxic Substances, EPA) and
Debbie Edwards, Ph.D. (Director, Office of Pesticide Programs)

10:40 a.m. **Meeting Administrative Procedures**
Paul Lewis, Ph.D. (Designated Federal Officer [DFO], HSRB, OSA, EPA)

10:45 a.m. **Meeting Process**
Celia Fisher, Ph.D. (HSRB Chair)

10:55 a.m. **EPA Follow-up on HSRB Recommendations**
Mr. William Jordan (EPA, OPP)

Completed Repellent Efficacy Studies: IR3535 Aerosol (EMD-003.3 and EMD-004.3)

11:10 a.m. **Science and Ethics of Repellent Efficacy Studies**
Clara Fuentes, Ph.D. (OPP, EPA) and Mr. John Carley (OPP, EPA)

11:50 a.m. **Public Comments**

12:15 p.m. **Lunch**

1:15 p.m. **Board Discussion**

EMD-003.3: Tick Repellency with Aerosol Spray Formulations

a. Is this study sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy of the formulation tested against ticks?

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

EMD-004.3: Mosquito Repellency with Aerosol Spray Formulations

a. Is this study sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy of the formulation tested against mosquitoes?

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

Carroll-Loye Mosquito Repellent Efficacy Protocol WPC-001

2:15 p.m. **Science and Ethics of Protocol WPC-001**
Clara Fuentes, Ph.D. (OPP, EPA) and Mr. John Carley (OPP, EPA)
3:00 p.m. **Break**
3:15 p.m. **Public Comments**
3:40 p.m. **Board Discussion**

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

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

Research Conducted After April 7, 2006: Meaning of "Substantial Compliance" with 40 CFR Part 26

4:40 p.m. **Meaning of "Substantial Compliance"**
Mr. William Jordan (OPP, EPA) and Mr. Keith Matthews (OGC, EPA)
5:00 p.m. **Public Comment**
5:20 p.m. **Board Discussion**
6:00 p.m. **Adjournment**

Thursday, April 19, 2007

8:30 a.m. **Convene Meeting**
Celia Fisher, Ph.D. (HSRB Chair)
8:40 a.m. **Follow-up From Previous Day's Discussion**
Mr. William Jordan (OPP, EPA)

Completed Patch Test Studies

8:50 a.m. **HSRB Workgroup and EPA Process on CBI Redacted Submissions**
Celia Fisher, Ph.D. (HSRB Chair) and Mr. William Jordan (OPP, EPA)

Part I. 48-Hour Dermal Irritation Patch Test

9:00 a.m. **Science and Ethics of 48 Hour Dermal Irritation Patch Test**
Roger Gardner, Ph.D. (OPP, EPA) and Mr. John Carley (OPP, EPA)

10:00 a.m. Public Comments

10:30 a.m. Break
10:45 a.m. Board Discussion

a. Is this study sufficiently sound, from a scientific perspective, to be used as part of a weight-of-evidence assessment to evaluate the potential of the formulations tested to irritate human skin?

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

12:15 p.m. Lunch

Part II. Repeated Insult Patch Test

1:30 p.m. Science and Ethics of Repeated Insult Patch Test
Roger Gardner, Ph.D. (OPP, EPA) and Mr. John Carley (OPP, EPA)
2:15 p.m. Public Comments
2:45 p.m. Board Discussion

a. Is this study sufficiently sound, from a scientific perspective, to be used as part of a weight-of-evidence assessment to evaluate the potential of the formulations tested to cause sensitization of human skin?

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

3:45 p.m. Break

Framework for Developing Best Practices for Subject Recruitment for Handler Exposure Research

4:00 p.m. Framework for Developing Best Practices for Subject Recruitment for Handler Exposure Research
Mr. John Carley (OPP, EPA)
4:30 p.m. Public Comments
4:45 p.m. Board Discussion

a. What additional elements of the process of recruiting and enrolling subjects in handler exposure research should be addressed in a “Best Practices Framework”?

b. For each of the elements in the “Best Practices Framework,” please identify any additional sources of guidance that could be useful for an investigator who is designing a process for recruiting and enrolling subjects in handler exposure research.

5:45 p.m. Adjournment

Friday, April 20, 2007

8:30 a.m. **Convene Meeting**
Celia Fisher, Ph.D. (HSRB Chair)

8:40 a.m. **Follow-up From Previous Day's Discussion**
Mr. William Jordan (OPP, EPA)

Follow-up on AHETF and AEATF Protocols

8:50 a.m. **EPA's Need for New Research on Occupational Handler Exposure**
Mr. William Jordan (OPP, EPA), Mr. Jeff Evans (OPP, EPA), Mr. Jeff Dawson (OPP, EPA), and Mr. Matthew Crowley (OPP, EPA)

10:00 a.m. **Break**

10:15 a.m. **EPA's Need for New Research on Occupational Handler Exposure (continued)**
Mr. William Jordan (OPP, EPA), Mr. Jeff Evans (OPP, EPA), Mr. Jeff Dawson (OPP, EPA), and Mr. Matthew Crowley (OPP, EPA)

11:15 a.m. **Summary of EPA FIFRA SAP January 2007 Report "Worker Exposure Methods"**
FIFRA SAP Chair and/or Designee

11:45 a.m. **Public Comments**

12:15 p.m. **Lunch**

1:15 p.m. **Board Discussion**

Recognizing that protocol-specific science and ethics issues will be addressed in later HSRB meetings, EPA has attempted to explain the basis for its conclusion that additional information on exposure for people who mix, load, and apply pesticides (handlers) would be useful in EPA's regulatory decision-making and therefore new research would be valuable. Do the materials provided by EPA regarding the quality of the scientific data currently available for assessing exposures for handlers contain useful information to establish the societal value of proposed new handler exposure research, assuming individual protocols would generate scientifically valid information?

What additional information, if any, would the Board want with respect either to handler research in general or to individual protocols?

2:15 p.m. **Adjournment**

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.