August 7, 2007

Minutes of the
United States Environmental Protection Agency (EPA)
Human Studies Review Board (HSRB)
June 27-29, 2007 Public Meeting
Docket Number: EPA-HQ-ORD-2007-0403
HSRB Web Site: http://www.epa.gov/osa/hsrb/

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

Dates and Times:	Wednesday, June 27, 2007, 11:30 AM – 6:15 PM Thursday, June 28, 2007, 8:30 AM – 5:45 PM Friday, June 29, 2007, 8:30 AM – 3:00 PM (See Federal Register Notice – Attachment B)
Location:	EPA, One Potomac Yard (South Bldg.), 2777 S. Crystal Drive, Arlington, VA 22202
Purpose:	The EPA Human Studies Review Board (HSRB or Board) provides advice, information, and recommendations on issues related to the scientific and ethical aspects of human subjects research.

Attendees:	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 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. William Brimijoin (Vice Chair, HSRB) introduced himself and stated that he would serve as Chair for this HSRB meeting. He welcomed Board members, U.S. Environmental

Protection Agency (EPA or Agency) staff, and members of the public to the June 2007 HSRB meeting and 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. At Dr. Brimijoin's request, Board members introduced themselves.

Welcoming Remarks

Dr. George Gray (Science Advisor, EPA) welcomed Board members and conveyed EPA's appreciation for their work in preparing for and participating in the HSRB meetings. He noted that the HSRB has influenced how EPA uses the results of research involving human subjects. Dr. Gray welcomed members of the public and his EPA colleagues and thanked Dr. Brimijoin for serving as Chair of this meeting. Dr. Gray introduced Ms. Susan Podziba, who will serve as facilitator during the HSRB meeting. Ms. Podziba is a public policy mediator and has worked with a number of other EPA and federal advisory committees.

Dr. Gray provided a brief overview of topics to be addressed during this meeting. The topics included a redacted Confidential Business Information (CBI) submission; Dr. Gray noted that he was pleased with efforts to develop a framework that permits sound scientific and ethics review of redacted CBI material at an open meeting. He indicated the science and ethics for protocols to measure exposure of occupational pesticide handlers would be discussed. The HSRB discussed plans to implement such protocols at the June 2006 and April 2007 meetings, and EPA appreciates the HSRB's advice on these matters.

Mr. William Jordan (OPP, EPA) explained that because of scheduling issues, Dr. Debbie Edwards (Director, OPP, EPA) was unable to attend the morning session. Mr. Jordan expressed EPA's appreciation for the HSRB's work and looked forward to a productive meeting. He outlined three sets of topics for discussion. The first topic involved two new repellent efficacy protocols, one submitted by Dr. Scott Carroll (Carroll-Loye Biological Research, Inc.) and the other by Insect Control and Research, Inc. (ICR). EPA also has obtained journal articles describing four completed toxicology studies from a public literature search performed in the course of gathering information for a risk assessment of a registered pesticide active ingredient. EPA seeks HSRB input on these studies because the Agency has proposed to use them for risk assessment activities for a re-registration review. Lastly, the HSRB will review major scientific and ethical issues in the design and conduct of proposed pesticide handler exposure studies.

Meeting Administrative Procedures

Dr. Lewis welcomed Board members and thanked them for their efforts in preparing for this meeting. 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 announcements of meetings in the *Federal Register*, and meeting materials made available at a public docket—are met. As DFO, he also works with the appropriate officials to ensure that all applicable ethics regulations are satisfied. Each Board member has filed a standard government financial disclosure form that has been reviewed by Dr. Lewis and the OSA Deputy Ethics Officer in consultation with EPA's Office of

General Counsel to ensure that all ethics disclosure requirements have been met. Dr. Lewis reminded participants that meeting times would be approximate and that public comments would be limited to five minutes.

Because of the rescheduled start time for this meeting, review and approval of the draft April 18-20, 2007 HSRB meeting report will be performed during a teleconference to be scheduled in late July or August 2007. A *Federal Register* notice will inform the public of the exact time and date of the teleconference.

EPA Follow-up on HSRB Recommendations

Mr. Jordan reviewed EPA follow-up on HSRB recommendations from the April 2007 meeting. Concerning the studies on the active ingredient IR3535 in an aerosol formulation, EPA has accepted and agrees with the Board's recommendation and will rely on data from these studies in its review of applications for registration of this product. Regarding the field mosquito efficacy protocol WPC-001, Dr. Carroll has revised the protocol according to HSRB and EPA recommendations. The field test will be completed in July 2007, and Dr. Carroll will prepare his report and submit it to EPA in time for review at the October 2007 HSRB meeting. The skin irritation study reviewed by the Board was deemed scientifically useful and ethically acceptable; EPA agreed with the Board's conclusions and is using the data from this study in the review of this product. The HSRB had concerns that the skin sensitivity study reviewed during the April 2007 meeting was not ethical. EPA agreed with this assessment and will not rely on the results of this research. EPA will require the product to carry a label instructing users to stop using the product and seek medical attention if they observe any skin irritation.

The HSRB suggested revisions of the document describing best practices for recruiting subjects for the Agricultural Handler Exposure Task Force (AHETF) protocols; EPA will incorporate them into the document. The Board also endorsed EPA's view that the research planned by the AHETF and Antimicrobial Exposure Assessment Task Force (AEATF) will be useful and provide important information for improving assessment of handler risk while mixing, handling, or applying pesticides. Further discussion on topics related to the activities of these task forces is scheduled during this meeting.

EPA Review of Carroll-Loye Protocol LNX-001

Introduction

Mr. John Carley (OPP, EPA) presented background information for Carroll-Loye protocol LNX-001, which proposed a field test of mosquito repellency for two conditionally registered formulations containing 20 percent picaridin as the active ingredient. The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) allows EPA to conditionally register such products; the condition for registration of these products is efficacy studies.

LNX-001 is adapted from and similar to other Carroll-Loye protocols for field mosquito repellency studies previously reviewed favorably by the HSRB. The initial submission met the standard of completeness as defined in 40 Code of Federal Register (CFR) §26.1125; EPA's

science and ethics review on May 24, 2007, was based on the initial protocol submission. Dr. Carroll proposed revisions to the protocol and informed consent forms (ICFs), which were approved by the Independent Investigational Review Board, Inc. (IIRB) of Plantation, FL on June 12, 2007, and provided to the HSRB on June 18, 2007. Copies of the IIRB-approved versions of the ICFs and a new IIRB-approval letter were submitted to the docket on June 21, 2007. Mr. Carley commended Dr. Carroll's responsiveness to HSRB recommendations, noting that the original protocol was submitted before the April 2007 HSRB meeting and revised quickly based on HSRB recommendations made at that meeting.

Scientific Considerations

Mr. Kevin Sweeney (OPP, EPA) provided the science assessment for LNX-001. The objectives of this protocol are to test the mosquito repellent efficacy of the test material to satisfy a registration condition imposed by EPA. The test materials are lotion (EPA Reg. No. 39967-50) and pump spray (EPA Reg. No. 39967-50) formulations containing 20 percent picaridin. The oral LD50 of picaridin is greater than 5,000 milligrams (mg) per kilogram (kg) and the dermal LD50 is greater than 2,000 mg/kg. The study includes a dosimetry phase involving 10 subjects to determine the typical consumer dose of each formulation for use in efficacy testing. The subjects are trained to aspirate landing mosquitoes before they bite, using laboratory-reared, pathogen-free mosquitoes. The study is not blinded.

Ten subjects will be treated with each formulation and two untreated control subjects will participate in each of two field trials. The untreated subjects are used to monitor mosquito pressure, and each subject will be accompanied by two technicians who will aspirate landing mosquitoes before they can probe or bite. Both treated and untreated subjects will be exposed to mosquitoes for 1 minute at a time every 15 minutes. The duration of efficacy is calculated as the average time from treatment to "first confirmed landing with intent to bite" (FCLIBe). The testing will be conducted at field sites in either the California Central Valley or Southern California (depending on season). Expected wild mosquito populations include *Aedes vexans*, *Ochlerotatus melanimon*, *O. taeniorhynchus*, *Culex tarsalis*, and *C. pipiens*. Variables to be measured include subject limb area and weight of test materials delivered to subject limb (lotion) or gauze dosimeters (spray) for the dosimetry phase. For the efficacy phase, biting pressure must be greater than or equal to one landing with intent to bite per minute. The test results will be analyzed by calculating the mean time to FCLIBe, with standard deviation and 95 percent confidence interval; depending on the results, other analyses also may be appropriate. Untreated controls will not be used for comparison of treatment means. Although the actual dose rate will not be known until the dosimetry phase is complete, using a conservative estimated typical dose of 1 gram (g) per 600 square centimeters (cm^2), the Margins of Exposure (MOE) for dermal toxicity is not expected to be less than and may be significantly greater than 750.

The sample size of 10 reflects a compromise between financial and scientific concerns; it also is recognized that sample size is difficult to pre-determine without knowing the distribution of outcome values. EPA guidelines recommend 6 replicates, which has been widely regarded as sufficient to show statistical significance at $P<0.05$. Use of 10 replicates slightly improves accuracy in estimating the population mean; however, each additional subject beyond 10 has a smaller affect on the precision of the mean. Nonetheless, EPA is reconsidering the issue of

sample size in light of the Board's advice on this subject at the January 2007 and April 2007 HSRB meetings. EPA will apply any new standards or requirements to future proposals; however, the Agency's current position is that a sample size of 10 treated subjects, which exceeds the size specified in the current draft guidelines, is acceptable for studies of this nature.

Deficiencies noted by EPA in review of this protocol include lack of an explicit hypothesis; lack of an explanation for using untreated controls in dosimetry; no information on diagnostic statistical tests for normality, or on how non-normally distributed data will be analyzed; and no justification for using Kaplan-Meier statistical analysis. Additionally, the exact locations of the four measured circumferences for determining limb surface area during the dosimetry phase should be recorded so that dosimeters can be placed in the same locations. These deficiencies were addressed in revisions to the protocol, which were submitted in the June 18, 2007 amendment to EPA.

As revised in the June 18, 2007 amendment, this protocol is likely to yield scientifically reliable information and produce important information that cannot be obtained except by research with human subjects. The protocol has clear scientific objectives and an explicit hypothesis; the study design should produce data adequate to achieve the objectives and test the hypothesis.

Ethical Considerations

Mr. Carley provided the ethics review of LNX-001. This study proposes to test the mosquito repellent efficacy of two test formulations in the field. Both test formulations are conditionally registered; registrants requested product-specific field efficacy testing to keep the products on the market. If demonstrated to be efficacious, these products present a potentially attractive alternative to other available repellents, some of which are considered unpleasant by many users.

Subjects will be recruited from among those who have participated in previous Carroll-Loye Biological Research repellent efficacy tests and/or have agreed or requested to be included in their volunteer database. The study excludes participants under the age of 18 years or over the age of 55 years, students or employees of the investigator, pregnant or nursing women, those sensitive to repellents or mosquito bites, those in poor health or physical condition, and subjects unable to speak and understand English. Two "experienced" subjects will serve as untreated controls in each field trial. No eligible subjects come from populations vulnerable to coercion or undue influence.

Risks include possible irritation to the eyes if contacted by the repellents and harm if swallowed, possible exposure to biting arthropods, and possible exposure to arthropod-borne disease. Risks from the test materials have been minimized by excluding sensitive candidates, closely monitoring the dosimetry phase, and having technicians 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 the field study in an area where mosquito-borne viruses have not been detected for at least a month, by minimizing bites, and by testing aspirated mosquitoes for

pathogens. The probability of risks is characterized as extremely small because of low acute and chronic hazard profiles of the products (although the lotion is a Toxicity Category II eye irritant), research is designed to minimize exposures, training subjects to aspirate landing mosquitoes before they have time to probe or bite, and field testing in areas free of West Nile Virus (WNV) for at least a month.

The primary direct beneficiary of these tests is the sponsor, and there are no direct benefits to subjects. If the materials are proven effective and remain on the market, indirect beneficiaries will include repellent users who prefer one of these products to other available repellents. EPA has found no reasonable opportunities to further reduce risk while maintaining scientific robustness; the residual risks to the subjects are very low and are reasonable considering the expected societal benefits to repellent users.

The Plantation, FL IIRB reviewed and approved the protocol and informed consent materials on April 5, 2007, and reviewed and approved the amendments to the protocol and ICFs on June 12, 2007. This IIRB is independent of the sponsors and investigators and registered with the U.S. Department of Health and Human Services' (HHS) Office for Human Research Protections (OHRP), but is not accredited by the Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP). There have been no changes in IIRB procedures since previous submissions to EPA and EPA has determined that they meet regulatory standards. Concerning recruitment and informed consent, the description of subject recruiting and consent processes is complete and satisfactory, as supplemented by the amendments dated June 18, 2007. An IIRB-approved ICF for both treated and untreated subjects was included in the original submission on April 10, 2007. A mark-up of separate ICFs for treated and untreated subjects and IIRB-signed final ICFs were included in the supplemental submission on June 18, 2007. Concerning respect for subjects, the methods proposed for managing information about prospective and enrolled subjects will generally protect their privacy. The June 18, 2007 amendment proposes to delete subject names from data collection forms, thereby improving protection of subject privacy. 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 pesticide laws. The primary ethical standards applicable to this research are 40 CFR Part 26, subparts K and L. A point-by-point evaluation of how this protocol, as submitted on April 10, 2007, addresses the requirements of 40 CFR Part 26, subparts K and L, and the additional criteria recommended by the HSRB appears as Attachment 1 to the EPA Review of May 24, 2007.

Several deficiencies were noted in the EPA review of this protocol, but these have been addressed in subsequent amendments to the protocol. Needed descriptions of how untreated controls will be recruited, and how the process of informing them will differ from that used for treated subjects were included in the June 18, 2007 amendments. An erroneous statement on page 7 claims that concentrations of the active ingredient in test materials are lower than previously registered products; however, the concentrations in question are actually higher and

this error still requires correction. To further respect subject privacy, data collection forms are reported to have been modified to delete subject name.

As modified, this protocol meets all requirements of 40 CFR §26.1111, §26.1116, §26.1117, §26.1125, §26.1203, and all elements of National Academy of Sciences (NAS) recommendations 5-1 and 5-2. If further revised to correct the remaining error, protocol LNX-001 will meet the applicable requirements of 40 CFR Part 26, subparts K and L.

Public Comments

Dr. Scott Carroll of Carroll-Loye Biological Research, Inc., and Dr. Ghona Sangha, Consultant, on behalf of Carroll-Loye Biological Research, Inc.

Dr. Ghona Sangha has worked with picaridin since its development and serves as a consultant to the registrant of the product. She attended this meeting to answer general questions concerning picaridin.

Dr. Carroll thanked the Board for its review of Carroll-Loye protocols and ICFs. He noted that in response to HSRB suggestions he has segregated the protocols for treated and untreated subjects. Dr. Carroll noted that, concerning the specific protection of pregnant or nursing women, these women could be included as untreated controls because they would not be exposed to the products. This issue was raised with the IIRB, although few such women are likely to participate.

Dr. Carroll stated that the issue of sample size should be discussed. His protocols currently use 10 subjects; historically, most scientifically sound studies of DEET were performed using only 6 subjects. He asked the Board for comments concerning statistical arguments to address this issue. Dr. Brimijoin noted that in his experience with small group animal experiments to demonstrate an effect, the primary aim was to determine whether a product was effective or not and roughly how effective. He asked whether this was the goal of the repellent efficacy studies or if the protocol sought to determine whether the results of the study would be applicable to the general population or if there would be subjects who would find the products to be ineffective or undesirable. Dr. Carroll explained that the protocols seek to determine a rough efficacy. It is known that any product effectiveness will vary between people; the goal of the protocol is reasonable precision for determining a minimum protection time.

Dr. Brimijoin asked Dr. Sangha for information concerning the irritancy or other toxicities of the 20 percent picaridin formulation, because this concentration of picaridin is higher than that found in similar products. Dr. Sangha responded that although picaridin is new to the United States, it has been used in Europe and Australia. Picaridin was developed based on chemical modeling to fit receptors found in the mosquito. Dr. Sangha stated that she served as Director of Toxicology for Bayer and was responsible for toxicology testing. Based on toxicology data, picaridin is safe for use even up to the highest doses tested, which were accompanied by only minor liver changes in rats. Dermal toxicity and teratology testing was performed using dermal application, and all results indicated that picaridin was safe. Picaridin

also has no neurotoxin potential and no cancer-causing properties have been noted. A complete packet of this information could be available and picaridin meets EPA safety standards.

Picaridin itself is not a significant irritant; however, many formulations contain ethanol, which can be irritating. Picaridin is efficacious compared to similar products and provides protection equal to or better than DEET. Picaridin also has a good skin feel and does not react with plastics, unlike other DEET products. Picaridin is not significantly dermally absorbed; less than 2 percent of applied product is absorbed by the skin. Picaridin is safe for use on all people, including children.

Dr. Janice Chambers asked OPP representatives whether efficacy studies are required for any new formulation of a substance. Mr. Sweeney responded that efficacy testing is required unless the formulation is substantially similar to a previously tested formulation. Dr. Chambers inquired how efficacy testing was performed in children if a label indicates that a product can be used on children. Mr. Carley noted that efficacy testing on children is not permitted. Mr. Jordan clarified that EPA expects a product that works well on adults will work equally well on children and thus does not require efficacy testing on children; adult data are used to evaluate efficacy. He explained that EPA used the data in the picaridin database described by Dr. Sangha to evaluate the range of exposures and possible effects on those exposed, including children. Information on developmental toxicity is available in this database, which EPA uses to determine whether young animals are more sensitive to picaridin than older animals. This information is used for risk assessment activities regarding safety in children, along with accounting for children's different body surface areas and weights. Dr. Brimijoin commented that if children are known not to be more sensitive to a compound, based on sound animal data, a 10-fold safety factor also usually is applied. Mr. Jordan explained that the Food Safety Act requires additional safety factors to account for the higher sensitivity of children. This applies to pesticides and to repellents only if the repellent is found on food. When performing risk assessments, EPA is mindful of the differences between exposure patterns in children and adults. If the data are insufficient to accurately characterize risk, EPA will include uncertainty factors.

Board Discussion

Scientific Considerations—LNX-001

Dr. Chambers opened the science review of LNX-001. She thanked Mr. Jordan for the memorandum framing the questions concerning this protocol and commended Dr. Carroll for continually improving the clarity of his materials. With respect to methods, this protocol is similar to previously reviewed protocols. While the scientific criteria are justified, the existing data are insufficient and new data are needed.

Five deficiencies were noted in EPA's review of this protocol. Dr. Carroll has addressed the lack of an explicit hypothesis in terms of time length of efficacy; explicit hypotheses are unnecessary for this type of research. He added an explanation of untreated controls and described modifications to the dosimetry protocol. Dr. Chambers also recommended that Dr. Carroll include limb surface area measurements in the protocol, as noted by EPA. Overall, the protocol is sound, similar to previous protocols submitted by Dr. Carroll.

With regard to sample size, a balance must be struck between practicality and risk; EPA should determine the appropriate sample size for these protocols. Although a larger sample size usually is preferred and there is little risk involved in this particular protocol, future protocols could involve increased levels of risk and perhaps expose unnecessarily large numbers of subjects to risk if EPA does not provide guidance. Dr. Chambers concluded that the protocol is sufficiently sound from a scientific perspective to assess the efficacy of these 20-percent picaridin formulations against mosquitoes.

Dr. Michael Lebowitz continued the scientific assessment of LNX-001. The protocol, with amendments, meets most HSRB scientific criteria; however, the safety considerations of the protocol would be strengthened by including an additional assay for pathogens in captured mosquitoes. The dosimetry phase also is a valuable addition to repellent testing protocols. Dr. Lebowitz agreed with Dr. Chambers regarding the hypothesis for this research. EPA statements concerning the representativeness of subjects are correct, and Dr. Lebowitz agreed with Dr. Chambers' assessments of the sample size issue. He expressed some concern regarding statistical comparisons using the untreated controls and the lack of positive or negative controls for the product matrix. Overall, the protocol is responsive to the HSRB charge.

Dr. Alicia Carriquiry commented on statistical issues related to this protocol. She clarified that the HSRB had not concluded that a sample size of 6 to 10 was inadequate, but rather that it is impossible to know whether this sample size is adequate or not. EPA should develop a way to weigh the risks and benefits of increasing sample size; however, EPA should not set a specific sample size because not all protocols will require the same sample size. The appropriate sample size for a protocol should meet criteria, such as power, and then be weighed against the risks to subjects; the Board understands that in some cases power may need to be sacrificed to mitigate risk. Dr. Carriquiry added that she appreciated Dr. Carroll's improvements to the protocols.

Dr. KyungMann Kim commented on recurrent themes in these repellant studies. He specifically expressed concern about the definition of "FCLIBe." The typical consumer will apply more repellant if bitten and will not wait for a second "confirming" bite to determine efficacy. Dr. Kim also stated that the way the data are analyzed presents problems. For example, if no bites are received during the course of the experiment, 15 minutes are added to the total time in the field and that is the point at which the event (biting) is considered to have happened. Censored survival methods would provide a better way to analyze this data, instead of using a normal distribution assumption for data that is not likely to be normally distributed.
Dr. Brimijoin inquired about the seriousness of Dr. Kim's concern regarding the basic measurement of FCLIBe. Dr. Kim explained that at the October 2006 HSRB meeting, data points were presented in which the subject experienced multiple landings, but these were not confirmed within 30 minutes by a subsequent landing and thus were not counted; Dr. Kim considered this to be a flawed approach for measuring protection time. Once this issue is resolved, the Board should consider the appropriate way to analyze censored observations. It should be recognized that the time to occurrence of an event does not follow a normal distribution, so using the mean and standard deviation to analyze the data is inappropriate.

Dr. Kim added that it is unclear how the Board should address this issue. Measuring confirmed bites is an established method in the repellency testing field because it is believed to reduce noise and variability. The Board should recommend that investigators preserve the raw data so that it can be analyzed appropriately, even retrospectively; investigators also should continue to provide the raw data to the Board for review. The use of FCLIBe may not reflect typical consumer use; therefore, it is inappropriate to provide information derived using this approach. Dr. Chambers stated that Board members should consider the need for consistency with past labels and the need to be fair across past and present products.

Mr. Jordan agreed that Dr. Kim's observations related to how best to design these studies and interpret the resulting data were important. EPA has a long history of evaluating such studies, and against this history, the Agency has developed labels in a particular way against a backdrop of pesticide products. Because of EPA's investment and discussions at HSRB meetings, EPA is revisiting established ways of performing insect repellent efficacy studies and is in the process of revising guidelines. EPA is examining the evidence and considering revision of guidelines concerning events indicating failure of efficacy (landing, probes, bites, or FCLIBe) and also how to analyze truncated data. Any changes will be required only prospectively at first, then an assessment of the significance of the changes will be made with respect to labeling to determine whether re-testing of old products or re-evaluation of old data is required.
Dr. Lebowitz noted that other analyses could change the minimum protection information provided to the consumer in what is likely to be a less conservative manner. The goal should be to protecting the consumer in the most conservative way.

Dr. Brimijoin summarized that the Board expressed general satisfaction with protocol LNX-001 and thanked Dr. Carroll for his responsiveness to Board recommendations. Minor deficiencies in the protocol were identified, but the protocol has many strengths, especially as amended. Dr. Carriquiry noted that statistical issues remain; determining a specific sample size is not the issue, but rather developing a strong basis for establishing sample size for a given protocol. EPA needs to develop a process based on criteria, such as power and risk, to advise sponsors and registrants.

Dr. Brimijoin noted that Dr. Kim pointed out that the basic unit of measure of failure of efficacy (FCLIBe) should be discussed to determine if this is optimal. Dr. Kim also raised questions concerning data analysis, which should not rely simply on means and standard deviations but instead should incorporate censored survival analyses. Although this problem is recognized, the benefit to ensuring consistency with historical means of determining efficacy also was recognized to be of interest for informing the consumer. The HSRB commended EPA for revisiting its data collection methods and considering proper statistical treatment of this data.

Ethical Considerations—LNX-001

Dr. Sean Philpott opened the ethics discussion of protocol LNX-001. He deferred to his scientific colleagues regarding the scientific validity of the study, noting that a study that lacks scientific validity cannot be ethical. He commended Dr. Carroll for his improvements to the protocol.

This is a combined dosimetry and efficacy study enrolling a total of 20 subjects in both phases, and also includes two untreated controls. The untreated controls will be experienced field workers or frequent participants in repellency studies. The untreated controls will be used to determine the ambient mosquito biting conditions in the field. An additional three alternative subjects have been enrolled in the case of withdrawal of primary subjects and to protect subject privacy in the case of a need to withdraw because of a previously undiscovered pregnancy or other condition. Dr. Philpott deferred to his colleagues regarding whether the sample size would provide sufficient power.

Concerning compliance with 40 CFR Part 26, subparts K and L, Dr. Carroll has submitted to EPA all information related to the conduct and review of the investigation. Concerning study design, the risks to subjects are minimal and justified by societal benefits, including the efficacy of picaridin and increased number of repellent choices for the public. The nature and likelihood of risks and side effects are clearly stated in the ICFs and amended protocols. The risks include reactions to picaridin or other test materials, exposures to biting insects, and exposure to arthropod-borne diseases. Reasonable attempts to minimize the risks have been made and a clear medical management plan was provided. Drs. Carroll and Sangha have provided toxicology data that indicate that subjects are unlikely to be at risk for adverse reactions. Reactions to mosquito bites are usually mild and easily treated with over-the-counter remedies. Appropriate efforts have been made to exclude those with a history of severe reactions to insect bites, and clear plans to manage severe reactions are in place. The protocol was designed to minimize actual bites by using FCLIBe as an indication of efficacy failure. Exposure to biting insects also has been limited. The field tests are planned for areas where known disease have not been detected by vector control agencies for at least 1 month. Mosquitoes collected during the field test will be analyzed using reverse transcription polymerase chain reaction to test for pathogens, and plans are in place to contact subjects if pathogens are detected. These precautions represent expected standards to ensure that subjects in repellency studies are protected against exposure to arthropod-borne diseases.

40 CFR Part 26, subpart L excludes pregnant and nursing women and children from the subject pool; pregnancy tests will be administered the day of the study to ensure exclusion of pregnant women. Confidentiality of subjects is protected and mechanisms are in place to minimize potential coercion, such as excluding students and colleagues of the investigator. Subject compensation is at a level considered unlikely to represent undue influence to participate. With the provisions provided in the amended protocol submitted to EPA on June 14, 2007, LNX-001 comports with 40 CFR Part 26, subparts K and L.

Dr. Richard Sharp agreed with Dr. Philpott's assessment of the ethics of LNX-001. He noted that the ICFs should clarify that the concentration of picaridin used in this protocol is higher than that contained by previously registered products; the protocol will use a 20-percent formulation of picaridin and previously registered products contain between 5 and 15 percent. This is a substantial increase in the amount of active ingredient and Dr. Carroll should specifically describe this difference to potential subjects. Dr. Jerry Menikoff agreed with Drs. Sharp and Philpott and had no further comments.

Mr. Carley clarified the number of subjects and whether this was stated incorrectly in the protocol. Ten subjects will participate in the dosimetry phase and will test both formulations. It is not clear, however, whether the same 10 subjects will participate in the efficacy phase. A total of 10 treated and 2 untreated subjects in each field study results in a total of 34 subjects, not including alternate subjects. Therefore, the characterization of "at most" 34 participants is accurate because some subjects could participate in both phases of the study. Dr. Philpott agreed to check this value. He assumed the group would be the same because volunteers for the field test would be trained in the laboratory to aspirate mosquitoes and identify FCLIBe. Dr. Carroll clarified that approximately 80 to 90 percent of the subjects participate in all phases of the trial; therefore, the total number of subjects will be low. He used the value of 34 to try to account for the maximum number of participants, but would consider changing this number to 37 or even 40 to accommodate alternates. All potential subjects receive training even if they do not participate in the dosimetry phase of the study; Dr. Carroll offered to state this more explicitly in the protocol.

Dr. Brimijoin summarized that Dr. Philpott had considered all categories of risk and found a favorable risk-to-benefit ratio. Appropriate attempts were made to minimize risks. This protocol also has innovations that further minimize risk, such as post-test analysis of captured mosquitoes for pathogens and notification of subjects if pathogens are detected. The HSRB has found this protocol to be ethical, but recommends including the clarification recommended by Dr. Sharp to emphasize to subjects the significant difference in the concentration of active ingredient in this formulation compared to those in existing products.

EPA Review of ICR Protocol G0590307001A044

Introduction

Mr. Carley provided background on protocol ICR A044, submitted on behalf of the sponsor and ICR, Inc., by toXcel on April 12, 2007. This protocol proposes a field study in two locations of the mosquito-repellent efficacy of two new un-registered formulations containing picaridin. The initial submission met the standard of completeness as defined in 40 CFR §26.1125. EPA's Science and Ethics Review on May 24, 2007, was based on the initial protocol submission.

In response to EPA's Science and Ethics Review on May 24, 2007, toXcel (representing the sponsor) submitted comments to the HSRB docket on June 18, 2007, noting three errors in EPA's review and promising numerous changes in the protocol and ICFs; however, toXcel's comments to the HSRB docket did not include all proposed language to accomplish the promised changes. Although much work is still required to address all deficiencies noted in EPA's Science and Ethics Review, EPA considers this protocol ready for HSRB review.

The sponsor has asserted a claim of confidential business information with respect to the identity of the sponsor and the concentration of the active ingredient in each product. A HSRB workgroup reviewed the redacted version prepared by the submitter and concluded that the redactions to protect the CBI from disclosure would not prevent the HSRB from reviewing the protocol.

Scientific Considerations

Mr. Sweeney provided the science review of ICR A044. The objective of this study is to test the field efficacy of two unregistered mosquito repellent aerosol formulations containing picaridin. The test materials include Product A and Product B, both of which are aerosol formulations containing picaridin at concentrations within previously registered ranges. The oral LD50 is greater than 5,000 mg/kg and dermal LD50 is greater than 2,000 mg/kg. The study does not include a dosimetry phase; instead, efficacy testing will be performed using the standard dose rate of 1g/600 cm^2, equivalent to 1.67 mg/cm^2, with an expected MOE greater than or equal to 926. One treatment will be applied to a 250 cm^2 area on each forearm of each treated subject—Product A on the right arm and Product B on the left arm. Only the subjects will be blinded.

The study design calls for 10 subjects plus 2 alternates who will be treated with both formulations, and 2 untreated control subjects, selected by lot, in each of two field trials. Untreated subjects are included to monitor mosquito pressure; each subject is exposed for up to 5 minutes every 30 minutes, or until experiencing 5 mosquito landings. Treated subjects are exposed to mosquitoes for 5 minutes every 30 minutes. Both treated and untreated subjects will move to a screenhouse between 5-minute exposure periods. To minimize the potential to remove the repellent, treated subjects will not cover the treated skin between 5-minute exposure periods. The duration of efficacy will be measured as average time from treatment to "first confirmed bite" (FCB). The protocol calls for 1 day of testing lasting up to 14 hours; subjects will spend a total of 6 days away from home, including travel days for each site.

The field test sites are located in Savannah, GA, and Pine Island, FL. Expected wild mosquito populations include *A. vexans*, *Psorophora ferox*, *O. infirmatus*, and *O. taeniorhyncus*. Measured variables include subject limb dimensions, mosquito pressure (landings greater than or equal to 1 per minute), whole body landing count, time of all bites, and time to FCB. The test results will be analyzed by calculating the mean time to FCB (TFCB), and the standard deviation and 95 percent confidence interval around the mean. Untreated controls will not be used for comparison of treatment means and results will not be compared between the two formulations.

ICR's rationale for sample size follows the EPA guideline recommending six replicates. An analysis by Rutledge and Gupta (1999) shows that a sample size of 10 or 11 is needed to achieve, with 95 percent confidence, a standard deviation not greater than 2 hours after 8 hours of testing. Thus, this study will involve 10 treated test subjects; two additional alternate subjects will be treated to help ensure a minimum number of 10 and will also aid in protecting the privacy of any subjects who withdraw.

Several deficiencies were noted in the EPA review of this protocol. The protocol lacked an explicit hypothesis; the June 18, 2007 response promised to add the hypothesis that test products will be effective for 8 to 12 hours. Information concerning diagnostic statistical tests for normality, or on how non-normally distributed data will be analyzed was not included in the initial protocol. The June 18, 2007 response explained that statistical analysis will be limited to the calculation of mean TFCB, standard deviation, and 95 percent confidence interval around the

mean, and that TFCB will be recorded as 12 hours for subjects who do not experience repellency failure. There was inadequate justification for excluding "outlier" results, but the June 18, 2007 response promised that outlier measurements would be included in determination of complete protection time (CPT). A direct reference to Good Laboratory Practice (GLP) regulations at 40 CFR Part 160 was needed; the June 18, 2007 response promised to add references to 4 sections of 40 CFR Part 160 (GLP regulations) to the protocol.

The June 18, 2007 response failed to address questions of distributions raised in the EPA review and the protocol has not yet provided information on diagnostic statistical tests for normality, and on how non-normally distributed data will be analyzed. Concerning GLP, EPA has asked for citation of all applicable sections in addition to the four mentioned in the June 18, 2007 response. Minimally, sections 160.33, 160.47, 160.51, 160.120, and 160.130 should be cited, and the best solution would be to cite and promise compliance with "all applicable requirements of 40 CFR Part 160."

If amended as promised in the June 18, 2007 response, and if an acceptable reference to GLP regulations and an adequate statistical analysis plan are incorporated, this protocol is likely to yield scientifically reliable information, produce important information that cannot be obtained except by research with human subjects, and produce adequate data to achieve the clear scientific objective.

Ethical Considerations

Mr. Carley presented the ethics review of ICR A044. The proposed study would test the mosquito repellent efficacy of two unregistered test formulations in the field. EPA requires formulation-specific efficacy testing to register the products and demonstration of field efficacy for these test products would contribute to making available potentially attractive alternatives to other available repellents, some of which are found unpleasant by users.

Subjects will be recruited from a database including previous subjects of similar ICR tests as well as friends and colleagues of previous subjects. The subject pool is characterized as being "as representative of potential repellent users as we are able to make it." Untreated control subjects will be selected by lot the night before the test, from the group of subjects who have traveled to the test site. Children or pregnant or nursing women are excluded, as well as those sensitive to repellents or mosquito bites, those in poor health or physical condition, those unable to speak and understand English, adults over the age of 65 years, and permanent full-time employees of ICR. No subjects will be drawn from populations vulnerable to coercion or undue influence. This protocol differs from the Carroll-Loye protocols in that the subjects live in different parts of the country, some near the test sites and some far from the sites. Because of this, participation will involve 6 days away from home for testing and travel, and subjects will be provided with airfare and hotel accommodations at the test sites. A group of 14 subjects are recruited, consented, and then convene at the test location. This includes 10 treated subjects, two untreated controls, and two alternate subjects; subjects serve as an untreated control only once. In addition to airfare, lodging, and payment for meals, subjects are compensated for participation; assuming a 14-hour test day and payment over 6 days, compensation is expected to be approximately $676.50 per subject. Although this appears high enough to warrant concerns

about inducement to participate, most of those in the volunteer database have participated in these types of studies before; therefore, the compensation is considered unlikely to affect their decisions to participate.

Potential risks arise from the repellents themselves; the materials are Toxicity Category II/III for eye irritation (Material Safety Data Sheets show "Warning" label). The protocol contains misleading references to Toxicity Category IV for certain effects of the active ingredient and misleading references to beneficial effects of the inert ingredients (i.e., skin benefits). The risk of allergic or irritation response from test materials are minimized by excluding sensitive candidates and monitoring subjects closely. The MOE for dermal toxicity for the formulations is at least 1,000.

Risks of allergic or irritation responses to arthropod bites also exist. These can be reduced by excluding candidates with a history of severe reactions to mosquito bites, minimizing the number of untreated control subjects, exposing untreated controls only long enough to confirm continued mosquito landing pressure, permitting intermittent exposure of only a small area of treated skin, instructing subjects to move away from mosquito-infested areas between exposure periods, covering treated skin after efficacy breakdown, teaming subjects in pairs to watch each other for landing mosquitoes, brushing away mosquitoes attempting to bite with fewer than all six of their legs on the treated area of skin, and treating subject (and staff) shoes with permethrin to repel ticks. Risk of reaction to insect bites could be further reduced by treating landings as evidence of efficacy breakdown.

EPA requires demonstration of efficacy of repellency of mosquitoes known to carry specific diseases, such as WNV, to substantiate related product claims. Thus, the sponsor must conduct field testing in areas containing these potential vector species. The principal carriers of WNV are not common at the test site, and risks of arthropod-borne diseases are reduced by conducting field tests in areas where WNV has not been detected by the local Mosquito Abatement District for at least a week. Risks could be further reduced with an improved medical management plan, provision for post-exposure follow-up, and by excluding subjects over 55 years of age.

The primary direct beneficiary of this research is the sponsor and there are no direct benefits to the subjects. If these materials are proven effective, indirect beneficiaries will include repellent users who prefer this product to other repellents. Concerning risk-benefit ratios, opportunities have been identified to further reduce risk while maintaining scientific robustness. If these risks are minimized, residual risks to subjects would be low. The test materials are likely to prove effective and, if minimized, risks to subjects are likely to be reasonable in light of the expected societal benefits to repellent users.

An independent ethics review was conducted by the Essex Institutional Review Board (EIRB), Inc. of Lebanon, NJ. This board reviewed and conditionally approved the protocol on April 2, 2007, subject to revision, and subsequently reviewed and approved amendments 1-8 on April 6, 2007, and reviewed and approved ICFs on April 9, 2007. EIRB is independent of the sponsors and investigators and is registered with OHRP but does not hold Federal Wide

Assurances (FWA) or accreditation by AAHRPP. EIRB procedures have been submitted directly to EPA under CBI claims; EPA has determined they meet regulatory standards.

Concerning the informed consent process, most subjects do not live near the ICR laboratory; therefore, recruiting and consent processes must rely heavily on telephone contacts and mailing of documents. It is unclear whether subjects reviewed the informed consent materials before traveling to the test site. EPA is working with ICR to ensure that subjects were permitted to review the materials before traveling so that they could make a fully informed decision about participation. The submission of April 12, 2007, included an Institutional Review Board (IRB)-approved ICF for each site meeting the requirements of 40 CFR §26.1116 and §26.1117. Inconsistent descriptions of the recruiting and consent processes in the protocol and ICF still require reconciliation. Methods for managing information about prospective and enrolled subjects have been proposed and will generally protect subject privacy. Subject names currently are included on data collection forms; deletion would improve protection of subject privacy. The procedure for protecting the privacy of candidates discovered to be pregnant at the test site needs refinement. Subjects will be free to withdraw at any time and medical care for research-related injuries will be provided at no cost to the subjects.

This is a proposal for third-party research involving intentional exposure of human subjects to a pesticide, with the intention of submitting the resulting data to EPA under the pesticide laws. The primary ethical standards applicable to this research are 40 CFR Part 26, subparts K and L. The protocol cites ICR policy of compliance with HHS rules at 45 CFR Part 46 and the "EPA model rule;" HHS rules do not apply to this study and the reference to the "EPA model rule" is unclear. A point-by-point evaluation of how the protocol as submitted on April 12, 2007 addresses the requirements of 40 CFR Part 26, subparts K and L and additional criteria recommended by the HSRB appears as Attachment 1 to the EPA Science and Ethics Review dated May 24, 2007.

Deficiencies noted in the EPA ethics review of this protocol include inclusion of subjects over 55 years of age; such subjects should either be excluded or their inclusion should be justified. The June 18, 2007 submission promises to cap participation at the age of 55 years if the HSRB agrees with EPA that to do so is warranted and would not scientifically compromise the study. ICR also was asked to clarify exclusion factors concerning employees—either exclude all employees (i.e., full time and part time) of ICR or the sponsor, or justify not excluding all of them and describe the specific safeguards in place. The June 18, 2007 submission also clarifies that all employees of the sponsor, of ICR, and of any other interested organization will be excluded; the protocol and ICFs still require amendment.

Other deficiencies pertain to the risk of mosquito bites. This risk could be further reduced by treating landings as evidence not only of biting pressure but also of efficacy failure. ICR was asked to explain and justify the emphasis on distinguishing landings from probes, probes from bites, and bites with six legs on treated skin from other bites. The June 18, 2007 response argues that bites are a "more reliable and rigorous" endpoint than landings, treated subjects will typically receive only two bites, TFCB is a recommended endpoint in EPA draft guidelines, risks are sufficiently reduced by other means, and TFCB is a necessary endpoint for "robust and reliable" test results. The June 18, 2007 response does not provide justification for

these fine distinctions. EPA also found that the risks of contracting an arthropod-borne disease could be further reduced by providing for post-exposure follow-up; ICR's June 18, 2007 response promises to add follow-up calls to subjects 2 weeks after testing, although the protocol still requires amendment. EPA recommended including a straightforward commitment to conduct this research in compliance with 40 CFR Part 26, subparts K and L; the June 18, 2007 response does not address this comment. ICR also was asked to provide a single, clear and authoritative description of the process of informing candidates and seeking their consent, and harmonize discrepant references to the process; the June 18, 2007 response indicates that discrepancies will be resolved through amendments to the protocol and ICFs. Regarding protection of subjects' privacy, ICR promises that subject names will be deleted from data collection forms in favor of subject identification codes and initials. EPA recognized that recruitment of alternate subjects provides some opportunity for discrete withdrawal without explanation, but may not be adequate to protect the privacy of subjects who are found to be pregnant only after traveling to the test area and participating in the evening-before-the-test activities; the June 18, 2007 response does not address this comment.

Concerning compliance with ethical standards, with EIRB approval of all requested revisions, all requirements of 40 CFR §26.1111, §26.1116, §26.1117, and §26.1125 would be met; requirements of 40 CFR §26.1203 are met. All elements of NAS recommendation 5-1 and 5-2 are satisfied. EPA concludes that, if revised as requested, ICR A044 and the associated ICFs will likely meet the applicable requirements of 40 CFR Part 26, subparts K and L. This research must not be initiated without EIRB approval of the revised protocol and ICFs.

Dr. Lebowitz inquired if efficacy testing using first bite was developed before WNV became prevalent. Mr. Carley responded that this was true. Dr. Lebowitz noted that this demonstrated the need for revisions in practices when new diseases become prevalent and human testing may lead to infection. He was uncertain how EPA or the Centers for Disease Control and Prevention (CDC) should respond to this, but current public health prudence suggests that this standard should be changed to prevent possible infection. Dr. Chambers asked what percentage of landings result in bites; neither Mr. Carley nor Mr. Sweeney could provide an answer. Dr. Susan Fish requested clarification of the difference between a bite with six legs contacting the skin versus fewer legs making contact. Mr. Sweeney explained that borders without repellent exist on the edges of the treated areas. Mosquitoes may land there and bite; these bites are not considered proof of failure of efficacy because the mosquitoes may be contacting areas not treated by the repellent. Dr. Chambers observed that the protocol states that such bites would not be counted and used to determine efficacy breakdown.

Dr. Kim noted that this protocol increases exposure time to 5 minutes, compared to 1 minute used in the Carroll-Loye protocols. He inquired whether this would have an impact on outcome, and if so, how the outcomes from the different protocols could be reconciled. Mr. Sweeney explained that each bite is considered an event, and if more events occur over time, a more accurate CPT calculation can be determined. More intervals and more endpoints will lead to more accurate data. EPA currently is working to reconcile these points as it addresses its guidelines for repellency testing. Dr. Carriquiry observed that although the ICF indicated that subjects will receive a maximum of two bites, subjects could receive more than two if the bites from mosquitoes that do not have a six-legged landing are not counted. Mr. Carley agreed, and

stated that this relates to whether a confirming event is needed to confirm efficacy. He explained that it is unlikely that a subject would receive a large number of bites that are all "unconfirmed." He agreed that the protocol and ICFs should contain a more carefully worded statement about the likely number of bites a subject may receive. The documents also should clarify that although subjects receive both products A and B, each independently-dosed arm is considered to be part of a different experience. Therefore, no fewer than two bites will be needed to indicate product breakdown. Problems arise if no bites are received before the end of the exposure period, and also if a subject is bit once at Hour 3 of the study but is not bitten again. It is difficult to accurately convey to potential subjects the maximum number of likely bites.

Dr. Lebowitz asked Mr. Sweeney if he was aware of the reliability of data concerning detection of arthropod-borne diseases at the test site and whether lack of detection for 1 week was sufficient to reduce potential exposure. Mr. Sweeney agreed that EPA did not know whether 1 week without evidence of pathogens provided sufficient protection. Dr. Chambers observed that this protocol followed current guidelines for efficacy testing more closely than the protocols submitted by Carroll-Loye; Mr. Sweeney and Mr. Carley agreed.

Public Comments

Mr. Niketas Spero and Dr. Robin Todd of ICR

Mr. Niketas Spero (ICR) noted that ICR has a long history of performing repellent efficacy studies which have received favorable review from EPA. He also explained that the ICR A044 protocol was designed using current EPA guidelines.

The dosing application rate used in this study was based on guidelines developed during the testing of DEET. The application rate of 1.67 mg/cm^2 provides complete coverage without run-off. This application rate has been used in multiple studies so that comparisons can be made. Concerning counting bites versus landings, current EPA guidelines call for determining the TFCB; this guideline also has been used for many studies. Repellency failure, as measured by landing, can be problematic. Not all landings result in a bite and most consumers will not notice a landing, but will notice mosquito probing or bites. To minimize risk, the protocol excludes those who are over-reactive to insect bites, sensitive to repellents, older than 55 years of age, or who are not in good health. Subjects are exposed to mosquitoes for 5 minutes every 30 minutes and also are provided with protective gear so that bites can occur only on the exposed area. Concerning exclusion of landings in which all six legs do not make contact, this is commonly used to measure repellency and ensure that results are not confounded by a mosquito contacting an area near, but not on, the area of repellent application. ICR depends on mosquito abatement agencies for information concerning the lack of arthropod-borne diseases in the test areas and tests only in disease free areas. ICR believes that all possible measures to reduce risk and gather sound data have been made.

Dr. Carriquiry noted that subjects are informed of their freedom to withdraw from the study, but asked whether ICR would continue to pay for the withdrawing subject's hotel stay or to change their ticket to return home. Mr. Spero explained that the company would do either; the subject could stay at the site at ICR's expense or ICR would pay to change the ticket.

Dr. Lebowitz inquired whether ICR would change its testing plans if local abatement agencies found infected mosquitoes 5 kilometers from the test site or found a positive mosquito 2 or 3 weeks prior, but not 1 week prior to the field study. Mr. Spero noted that the presence or absence of arthropod-borne pathogens can change quickly. He was unsure of the value of monitoring for the presence of pathogens for an entire month. Monitoring for 1 week prior to and during the test likely minimizes the risk of disease transmission. Dr. Lebowitz noted that the protocol did not indicate what ICR would do in the event of a positive test result and that if a test site is positive 2 weeks before the study but negative 1 week before the study; the likelihood that pathogens are present during the week of testing is high. He also questioned how close the test site was to monitor for pathogens, for example, whether it was within the range of all mosquitoes that could carry WNV. Mr. Spero explained that monitoring is performed on a county-wide basis; he agreed that ICR would consider monitoring for more than 1 week.

Dr. Carriquiry questioned how the results obtained from the two different test sites would be analyzed, particularly if the efficacies at each site were significantly different. Dr. Robin Todd (ICR) responded that, when this has occurred in the past, ICR submitted the data as two different reports to EPA. EPA used the shorter measurement of efficacy for labeling purposes.

Dr. Chambers inquired whether Dr. Todd or Mr. Spero knew what proportion of landings resulted in bites; neither Dr. Todd nor Mr. Spero could answer this. Dr. Chambers also asked about the fraction of bites from mosquitoes landing partly on the gauze rather than entirely on the skin. Mr. Spero explained that this was unknown because such mosquitoes would be dislodged from the subject. ICR does not want to evaluate mosquitoes that have discovered a way to avoid the repellent but still bite. He added that over the course of an 8-hour day, the bandage may abrade away the repellent. Dr. Chambers questioned the number of times confirmed bites are received using a 5 minute exposure every 30 minutes. Mr. Spero noted that this was a new procedure for ICR; in the past, subjects were exposed continuously. He added that once a subject receives two bites, exposure of the treated site is halted.

Dr. Gary Chadwick questioned why two sites will be used for testing. Mr. Spero replied that EPA recommends testing at two different sites populated by different genera of mosquitoes.

Board Discussion

Scientific Considerations—ICR A044

Dr. Chambers opened the scientific discussion of ICR A044. She commended the authors for a clearly written protocol. She noted that the need for data arising from this study is justified. Several deficiencies were noted by EPA. The need for an explicit hypothesis is not significant for this type of research, as discussed for the protocol LNX-001. Dr. Chambers declined to comment on issues of statistical analysis. She concurred with EPA on subject exclusions and deemed the references to GLP to be reasonable.

Consistency is an issue for this protocol. The guidelines define bites as failure of efficacy, and the protocol is responsive to these guidelines; however, the Board has heard that counting

FCLIBe provides a greater measure of safety. Scientifically, landing with intent to bite provides a more conservative estimate of efficacy and thus is more protective for the consumer. The HSRB requests that ICR consider counting landings rather than bites. Concerning dosing, this protocol does not include a dosimetry phase but instead relies on established guidelines for dosing. Dr. Chambers recommended that a dosimetry study be performed before the field study and that the dose established by this work then be used. Mosquitoes also should be collected during testing and assayed for the presence of pathogens. The Board understands ICR's rationale for counting only six-legged landings; however, a more conservative measure of efficacy would count landings with fewer than six legs. ICR allows for collection of information on the total number of landings, but the value of this activity is unclear.

Dr. Chambers concluded that, in general, this is a sound protocol, but suggestions such as testing captured mosquitoes for pathogens and performing a dosimetry study would benefit the protocol, along with EPA's suggestions. EPA must decide whether landings or bites should be counted in tests of repellent efficacy and should develop guidelines reflecting this decision.

Dr. Lebowitz commended Mr. Carley and Mr. Sweeney on their reviews of the protocol. He stated his concerns about the adequacy of testing using bites, and how public health law would impact EPA given current WNV concerns. He suggested that EPA search for policies or decisions made by the CDC regarding this issue. It may be prudent for EPA to change its guidelines regarding the use of bites versus landings for efficacy testing. He commended the protocol's use of 5-minute exposure times every 30 minutes and providing a screened area for subjects when not exposed. Dr. Lebowitz agreed with EPA's and Dr. Chambers' critiques of the protocol.

Dr. Carriquiry stated that proposing to compute the mean and confidence interval of the data is inappropriate unless the data are normally distributed. Data should be collected and its distribution analyzed before plans for analysis are made. To state that the standard deviation is estimated to be 2 with a 95-percent confidence interval would imply a mean CPT of between 4 and 12 hours, which probably is not what the investigators intended. Dr. Carriquiry agreed with Dr. Chambers about EPA's need to decide whether to count bites or landings as failure of efficacy. The LNX-001 protocol would be at a disadvantage if its data were compared to that of this protocol, because landings with intent to bite likely occur before a bite, resulting in a comparably poorer measure of CPT.

Dr. Brimijoin agreed with the need for consistency across studies regarding bites versus landings. If the intent of these protocols is to generate data for labeling purposes, this discrepancy is unfortunate. EPA should quickly decide which standard to use. Using landings is protective of subjects and may be as robust as bites, but is likely to yield a different CPT.
Dr. Brimijoin acknowledged the questions raised by Dr. Lebowitz regarding checking test site mosquitoes for pathogens but considered the protocol to be adequate in this regard.
Dr. Carriquiry raised important issues focusing on determining the nature of the distribution of the data before deciding on the analyses to perform. The Board also recommended that dosimetry be performed before testing is implemented.

Ethical Considerations—ICR A044

Dr. Philpott opened discussion of the ethical considerations of ICR A044. He agreed with Mr. Carley's review and recommended that all Mr. Carley's suggested changes be made to bring the protocol into regulatory and ethical compliance.

Regarding the issue of landings versus bites, from an ethical perspective minimizing risk by using landings takes precedence unless there is a scientific justification indicating that using bites is more appropriate. If mosquitoes are collected, tests to detect the presence of pathogens are not difficult and should be performed. The investigators should provide more detailed procedures for monitoring subjects post-test to ensure that subjects have not been infected. Other concerns relate to the provision of EIRB procedures described in the minutes that were submitted as CBI; the Board must rely on Mr. Carley to assure the adequacy of these procedures because the redacted minutes provided to the Board were weak and difficult to assess. Because of this, it is difficult for the Board to determine whether the EIRB was qualified and adequately considered all ethical issues.

With respect to study design, subject risks arise from exposure to the test materials, bites from insects, and exposure to arthropod-borne diseases. Adequate stopping procedures are in place to minimize and respond to reactions to test compounds. Dr. Philpott expressed concern that the materials were described as Toxicity Category IV, although the materials are Toxicity Category II/III for acute or ocular exposure. Dr. Philpott assumed that these statements would be corrected based on the June 18, 2007 response. The issue of counting landings versus bites is relevant with regard to reactions to bites; however, most mosquito bites are minor and over-the-counter remedies are provided to participants to combat minor reactions. Exclusion of subjects with previous reactions to bites or skin care products further mitigates risk. To minimize exposure to disease, the protocol proposes proceeding only if no disease is detected for at least 1 week before field testing occurs. ICR believes that disease-free conditions for 1 month are unnecessary; however, a negative result the week before testing does not necessarily mean that pathogens are not present at the time of the field test. Establishing a temporal pattern of lack of disease in test areas, perhaps through weekly monitoring for a month, would provide better protection of subjects.

The ICFs discussed these risks with subjects by describing specific diseases present in each area in 2006. The forms also indicate that no human cases of specific disease were detected; this is deceptive because it refers to human disease, not to pathogens present in mosquitoes. Also, including the statement concerning conditions in 2006 is misleading and may inappropriately minimize the participants' perceptions of risk. This statement should be deleted and replaced with a detailed description of risk, symptoms of possible arthropod-borne diseases, and plans for monitoring and follow-up. The need to exclude pregnant women raises issues of protecting confidentiality if a subject tests positive for pregnancy after travel to the test site. The HSRB is unable to provide a solution for this, except perhaps use of a self-conducted test before travel.

Dr. Philpott commended ICR on addressing the issue of exclusion of ICR family members and part-time and full-time employees. He recommended that ICR add descriptions of

the informed consent process. Current documents explain that subjects will initially be contacted by telephone and states that the investigators will review the specifics of the studies with the subjects, but it is unclear whether another discussion of the risks and benefits of participation or methods of the study is held. Informed consent is a process and investigators should constantly discuss risks and benefits with subjects. Considering the selection of untreated controls by lot, a clear discussion of the greater risk to untreated controls should be provided in the ICF documents. The lottery approach to selecting controls also could be reconsidered.

Dr. Sharp noted that using landings as indications of efficacy failure appears to be more appropriate and minimizes risk. He asked whether the need to travel to a distant site for testing would hurt the ability of subjects to withdraw from the trial once they are at the site; this could establish a potentially coercive situation. Given the small number of subjects, local recruitment might provide a better alternative and would be better from an ethical perspective because of decreased potential for coercion.

Dr. Menikoff agreed with Dr. Philpott concerning resolution of the issue of landings versus bites. The ICFs need revision, including descriptions of how untreated controls are selected and a subject's chance of being selected as an untreated control. Dr. Menikoff was less concerned about coercion because ICR stated their willingness to pay for subject accommodations or travel expenses even if the subject withdraws from the study at the site. Dr. Lebowitz added that the Board should recommend participants be limited to those under 55 years of age.

Dr. Chadwick agreed with his colleague's assessments. He asked whether a more conservative measure of CPT was in fact more protective of consumers, because it might prompt consumers to apply the product more frequently, thus exposing themselves to greater amounts of chemicals. He also echoed Dr. Sharp's concerns about the preference for flying participants to a distant site rather than recruiting locally. He stated that there is no apparent scientific justification for the travel, and without this, there can be no ethical justification of travel. He added that although EPA prefers tests to be conducted in different areas, in his opinion the two sites selected for this study are not sufficiently different to meet this preference.

Dr. Chambers noted that the protocol indicates that landing mosquitoes will be dislodged from untreated controls; therefore, risk to the untreated controls is less than risk to treated subjects. Dr. Philpott agreed and reiterated that the risk to untreated controls must be clarified. Using experienced subjects with a greater appreciation of the risks involved as untreated controls could be considered. Dr. Chambers also commented on the travel issue, noting that ICR chooses its subjects from a pool of previous participants who have experience with similar protocols. Because these people are more cognizant of what is required for these tests, they are less likely to be coerced to participate than a naïve local volunteer. She added that if the mosquito species at the two sites are different, this justifies the use of distant sites.

Dr. Brimijoin asked the Board to indicate whether issues surrounding travel should be considered major or minor. Dr. Fish responded that she understood Dr. Sharp's concerns, but that Dr. Chambers' point about experienced subjects also should be considered. Justification by the investigators for use of distant test sites would be helpful. The use of experienced subjects

could result in better data and such subjects may be less open to undue influence because of their experience with similar studies. The transportation issue would therefore be less of a concern. Dr. Philpott clarified that two issues—travel and compensation—could be considered undue inducement. He speculated on whether being at the site and staying in a hotel would coerce subjects to remain in the study or to withdraw in hopes of participating in more interesting activities at the site than the testing. He stated that, in his opinion, the Board should err on the side of assuming that these are experienced volunteers and are likely to make sound judgments concerning their participation. Dr. Brimijoin asked Dr. Sharp to indicate whether he considered the travel issue to be a significant problem and to describe how the protocol could be revised to address the issue. Dr. Sharp responded that if ethics require maximizing a subject's ability to withdraw, testing at the distant sites could make this more difficult and an alternate design (i.e., use of local volunteers) should be considered. The subjects also participate in the study for 6 days, which is longer than if local volunteers were used. Traveling to distant sites also carries the risk of flying and of health issues unrelated to the study arising in a subject far from home. Using local volunteers would maximize subjects' ability to withdraw and minimize other travel-associated risks. Dr. Brimijoin noted that early versions of a Carroll-Loye protocol described having subjects travel to a potential distant test site; this would seem to imply a perceived benefit in relying on experienced subjects or difficulty recruiting suitable subjects at the test site. The value of experienced subjects versus the risks of travel must be considered. Dr. Brimijoin concluded that the Board's consensus is that there is concern about the ability of subjects to withdraw from the study held at a distant test site; ICR should consider the advantages and disadvantages of using local volunteers.

Mr. Carley clarified EPA's requirement for testing in two areas. Investigators also may choose multiple sites based on the times of year during which the study will be performed to maximize the presence and activity of relevant mosquito species. In response to a question from Dr. Chadwick, Mr. Sweeney clarified that the Florida site is mangrove swamp and the Georgia site is a more open habitat. The mosquito species present at each site are different. Testing is not performed in ICR's home state of Maryland because there are insufficient sites with consistently high biting pressure. Additionally, many of these areas are located in national or state parks and special permits would be required to test at these sites. The mosquito season is longer in the southern states and better biting pressure exists.

Dr. Carriquiry asked whether, given EPA guidelines indicating use of TFCB for efficacy studies, EPA could now request that investigators use time to first landing instead. Mr. Jordan clarified that the guidelines are recommendations and are not requirements that companies or EPA must follow. Those involved in repellent testing understand that much discussion is occurring around this issue and that EPA is currently trying to determine the best choice of endpoint. The Board's opinion appears to indicate that use of landings is ethically defensible, scientifically acceptable, and results in a more conservative endpoint and thus may be preferable to using bites. If EPA concurs, this change will be communicated to the relevant investigators. Mr. Carley added that any changes in guidelines would be implemented in a prospective manner.

Dr. Philpott was in agreement with Mr. Carley regarding deficiencies in the protocol. The issue of the use of landings or bites as endpoint is under consideration by EPA. The Board expressed concerns that a more detailed protocol to conduct analysis of the presence of

pathogens in the relevant mosquito populations and a plan for informing subjects if disease is detected are needed. Several Board members expressed concern that the absence of arthropod-borne pathogens for 1 week prior to the study is inadequate and a larger continued period of monitoring is desirable. Concerning informed consent, the investigators should focus more fully on the consent process and ensure that continued discussion and revisiting of risk with subjects occurs. The ICF appears to minimize risk because it refers only to human cases of disease and not to positive mosquitoes; this statement should be changed to more clearly reflect true risk. ICFs for subjects and controls should be separated because each group has different risks. Issues of confidentiality regarding pregnancy tests for subjects should be clarified. Regarding the requirement of travel to the test site, this may not be coercive but does complicate subjects' ability to withdraw. Further justification of this aspect of the study design or a different recruitment plan (i.e., local volunteers) may be needed.

Mr. Carley clarified that, concerning separate ICFs for subjects and controls, controls are not initially identified but instead are chosen by lot just prior to commencement of testing. Because landings are considered the endpoint for controls and bites for treated subjects, Mr. Carley recommend using landings as evidence of repellency breakdown; if landings are sufficient to measure biting pressure, they also should be sufficient to measure breakdown.

Dr Brimijoin summarized the ethical discussion by commenting that the Board review had been thorough and largely agreed with Mr Carley's analysis of minor deficiencies that need remedying and were actually in the process of being remedied. Among these were the need for more detailed protocols for conducting analysis of virally positive mosquitoes and how the resulting information will be transmitted and used. Also mentioned in the summary were issues relating to the use of multiple test sites and the travel involved, the need for separate consent forms for control subjects, a recommended age limit of 55, and the appropriateness of measuring landings versus bites.

Day 2 Opening Remarks

Dr. Edwards expressed her appreciation for the Board's work and its importance to OPP. She recognized the difficulty of the HSRB's tasks; discussing tests of potential toxins on humans is bound to be controversial and complicated. She commented that she would be attending an interagency conference on migrant worker and farm worker exposure to pesticides and the importance of protecting these workers to the fullest possible extent. Sound risk assessment requires using the best science and ethics available and OPP is interested in ensuring that it has the best possible data for its work. Dr. Edwards also commented on the importance of the Board's work in helping EPA ensure the scientific and ethical validity of research to test repellent efficacy, which is important for public health.

Follow-up Comments

Mr. Jordan thanked the Board for the previous day's discussions. EPA had no follow-up questions at this time.

Acrolein Inhalation Studies

Introduction

Mr. Carley provided background information on acrolein inhalation studies by Weber-Tschopp et al (1977). EPA seeks to use information from this article to assess human risk resulting from potential acute inhalation exposure to acrolein. Acrolein is a strong irritant that is used as a biocide to control growth of underwater plants, such as algae and slime growth in irrigation canals; it also has modest use as a pesticide. Acrolein is a chemical intermediate in the production of methionine, acrylic acid, and acrylates. The article, *Experimentally Induced Irritating Effects of Acrolein on Man*, (unpublished English translation of "Experimentelle Reizwirkungen von Akrolein auf den Menschen") by Weber-Tschopp, A.; Fischer, T.; Gierer, R.; and Grandjean, E. published in *International Archives of Occupational and Environmental Health* 1977 (40): 117-130 contains three sub-studies that will be discussed regarding EPA's use of the information contained therein for risk assessment studies. This work was conducted in the mid-1970s at the Institute for Hygiene and Occupational Physiology, Swiss Federal Engineering College, Zurich. The investigators were active in studies of tobacco smoke and the study was funded by the Swiss Association of Cigarette Manufacturers. The investigators are no longer active at the Institute.

The three sub-studies examined: A) continuous exposure to acrolein concentrations increasing over 40 minutes from zero to 0.60 parts per million (ppm); B) 90-second exposures separated by 8-minute recovery periods to concentrations increasing from 0.15 to 0.60 ppm; and C) continuous exposure over 60 minutes to constant concentration of 0.30 ppm. All sub-studies were conducted in a 30-cubic meter (m^3) chamber and the subjects were described as "healthy college students." Subjective measures of annoyance were subject responses to questions about air quality ("good", "acceptable", or "poor"), a wish to leave the room ("no", "don't know", or "yes"), and perceived eye, nose, and throat irritation (1=not at all; 2=a little; 3=medium; 4=strong). Objective measures of response were recorded only for tests A and C and included measurement of eye blink rate for two subjects in each group of three subjects and respiration rate and depth for the remaining subject in each group.

Scientific Considerations

Dr. Abdallah Khasawinah (OPP, EPA) provided the scientific assessment of the acrolein study. Acrolein is an acrylic aldehyde that is highly reactive and highly toxic by all routes. It can cause significant irritation and participates in lipid peroxidation and metabolism of α-hydroxyamino acid. Acrolein is highly volatile with a low boiling point. Because it is highly water soluble, acrolein is suitable for use as a pesticide in irrigation canals.

Exposure to acrolein in the Weber-Tschopp experiments took place in a large ($30m^3$) climatic chamber. Acrolein was vaporized and blown into the chamber using a carrier gas, and measurements were taken to confirm the acrolein concentration in the chamber. Three subjects were exposed at a time for Tests A and C and four subjects were exposed for Test B. Subjective irritation and annoyance were evaluated based on graded responses to questions (Tests A, B, and

C), blink rate (Tests A and C), and respiratory rate (Tests A and C). Respiratory rate was measured during the entire test and the mean value for 3-minute periods was reported.

Test A involved continuous, 40-minute exposure to increasing concentrations of acrolein. The test exposed 31 male and 22 female subjects, in groups of three. The initial acrolein concentration was 0 and rose continuously to 0.60 ppm after 35 minutes. Subjective annoyance/irritation questions were posed every 5 minutes and the blink rate was measured for two subjects in each group every 5 minutes; respiratory rate was measured continuously for the third subject. The results of Test A indicated that subjects experienced eye irritation at 0.09 ppm, nose irritation at 0.26 ppm, throat irritation at 0.43 ppm, elevated blink rate at 0.26 ppm, and depressed respiration (by 25 percent) at 0.60 ppm.

Test B involved intermittent exposures to increasing concentrations of acrolein. It is unclear whether the same subjects who participated in Test A also participated in Tests B and/or C. In Test B, 17 male and 25 female subjects, in groups of four, experienced 1.5-minute exposures to acrolein at 0 (control), 0.15, 0.30, 0.45, and 0.60 ppm. The subjects were permitted an 8-minute recovery period in a well-ventilated room between exposures and were asked the subjective evaluation questions after each exposure. The results of Test B found that the subjects experienced eye irritation at 0.30 ppm and nose irritation at 0.60 ppm, but no evidence of throat irritation.

For Test C, 21 male and 25 female subjects in groups of three were exposed to a constant concentration (0.30 ppm) of acrolein for 1 hour. Measurements were taken initially (0 ppm control) and throughout the exposure period as in Test A. Subjective questions were asked every 5 minutes, eye blink rate was measured every 5 minutes (two of three subjects), and respiration was continuously monitored (one of three subjects). Test C found that subjective irritation responses rose sharply over 20 minutes and then reached a plateau. The blink rate doubled after 10 minutes and then plateaued, and the respiratory rate decreased 20 percent after 40 minutes of exposure.

From these three tests, the authors concluded that the average threshold of irritation sensations ranged from 0.09 ppm (eye irritation) to 0.30 ppm (respiration rate and throat irritation), with nasal irritation at 0.15 ppm. Irritation was significantly stronger in the event of continuous exposure and no adaptation to the effects was observed.

EPA also considered an animal study of sub-chronic acrolein exposure to compare the sensitivity of different species to this irritant. Feron, et al (Integrated Risk Information System [IRIS] pg 27, 1978) exposed 20 hamsters, 12 rats, and four rabbits per sex per dose to different concentrations of acrolein. Concentrations of acrolein were 0, 0.4, 1.4, or 4.9 ppm and exposure was for 6 hours per day, 5 days per week, over 13 weeks. The results of this study found that the highest dose (4.9 ppm) resulted in all animals closing their eyes, hamsters experienced increased salivation and nasal discharge, and rabbits showed evidence of sneezing and breathing difficulties. Rats had bristling hair; six of these animals died. Depressed growth and diminished food intake was observed in rats and animals at the mid- and high-level doses. Changes in organ-to-body weight ratios (lungs, hearts, kidneys, adrenal glands) were observed at high doses, and hematological effects were noted in female hamsters (increased red blood cells, packed cell

volume, hemoglobin, and lymphocytes; decreased neutrophilic leukocytes) at high doses. The lungs of the rats that died had evidence of hemorrhage and collapsed dark reddish-purple areas. Histopathological findings in the respiratory tract indicated destruction and hyper- and metaplasia of the epithelial lining accompanied by acute and sub-acute inflammation in the nasal cavities of rats at all doses and in rabbits and hamsters at 4.9 ppm; trachea and larynx of rats and hamsters at 4.9 ppm; and in the bronchi of rats and rabbits at this dose. At the lower dose (1.4 ppm), hamsters and rats fell asleep and rabbits sneezed; there was decreased body weight gain and diminished food intake in rats and rabbits. No abnormal behavior was observed at 0.4 ppm, which was thus determined to be a "minimal" lowest observed adverse effect level (LOAEL), based on nasal effects in rats.

The IRIS evaluation of this work determined a reference concentration (RfC) for chronic exposure derived from the Feron et al study LOAEL of 0.4 ppm causing nasal effects in rats. Adjusting for exposure duration and to human equivalents, and applying a 1000X uncertainty factor, the RfC is 0.00002 mg per cubic meter (m^3). A chronic RfC of 0.00002 mg/m^3 is equivalent to 0.000009 ppm. Starting from the Weber-Tschopp human study, an Agency for Toxic Substances and Disease Registry (ATSDR) evaluation derived an acute-duration Minimum Risk Level of 0.003 ppm based on nose and throat irritation and decreased respiratory rate at a LOAEL of 0.3 ppm and uncertainty factors totaling 100. Comparison of human and animal studies found that humans are more sensitive to the irritating effects of acrolein and the minimal concentration for acute irritating effects in humans (ocular) was lower (0.09 ppm for humans versus 0.4 ppm for nasal irritation in rats, 1.4 ppm for hamsters, and 4.9 ppm for rabbits).

The Weber-Tschopp et al study provides the most suitable point of departure for acrolein risk assessment activities because it involved large numbers of healthy young subjects, used multiple exposures, and confirmed exposure concentrations analytically within 10 percent. Shortcomings of this study include use of subjective evaluations, lack of blind controls, and biased reactions; these are considered by EPA to be minimal. This work also determined that ocular effects are the most sensitive indicator of irritation and are also seen in the animal studies summarized in the ATSDR and IRIS reports. The evidence shows that humans are more sensitive to acrolein than experimental animals.

Based on this analysis, EPA concludes that 0.09 ppm (0.2 mg/m^3) is the minimal threshold for ocular irritation in humans and is the appropriate point of departure for assessing acute exposures. Uncertainty factors of 10X for intraspecies variability and 3X for "minimal" threshold are appropriate.

Dr. Lois Lehman-Mckeeman inquired how the odor threshold of 0.16 ppm was determined. Dr. Khasawinah responded that this was not specifically stated and speculated that perhaps a middle value was selected. Dr. Lehman-Mckeeman questioned how acrolein usually is used, given that these studies examined acute exposures. Dr. Khasawinah explained that EPA is assessing the effects of acrolein in water on bystanders, including agricultural workers, because of potential evaporation. Ms. Becky Daison (OPP, EPA) explained that acrolein is injected below the water surface in canals, but there is evidence of ambient concentrations. EPA's concern is the effects of this on workers, who can spend between 15 minutes and 8 hours applying acrolein to water; exposure during set-up and take-down also is an issue. EPA also is

concerned about use of acrolein in canals near residential areas because of potential evaporation and off-gassing. EPA is concerned about the duration of exposure during the application process and speculates that most canals would be treated on 26 days over the course of a year, exposing workers to short-term intermittent exposures 3 to 4 times a year. In response to a question from Board member Dr. Suzanne Fitzpatrick, Ms. Daison explained that the maximum level of acrolein in water is 15 ppm, but this value depends on the plants present in the water and physical parameters, such as flow rate. Dr. Brimijoin inquired how the data are used, given the discrepancy between acute human exposures with a low LOAEL and higher sub-chronic exposure limits in animals. Ms. Daison explained that the durations of exposure in the human studies more closely mimic real-life use of acrolein, so these values are more appropriate to use when modeling exposure.

Ethical Considerations

Mr. Carley provided the ethics review of the Weber-Tschopp et al study. The EPA ethics review on May 22, 2007 considered the publication Weber-Tschopp, A.; Fischer, T.; Gierer, R.; and Grandjean, E. (1977) Experimentally Induced Irritating Effects of Acrolein on Man (unpublished English translation of "Experimentelle Reizwirkungen von Akrolein auf den Menschen") *International Archives of Occupational and Environmental Health* 1977 (40): 117-130. This is a report of third-party research involving intentional exposure of human subjects that measured toxic endpoints. The research was not conducted with the intention to submit it to EPA under the pesticide laws. EPA retrieved the article from the published literature; it has not been submitted by a regulated entity. Because the document was not submitted to EPA, 40 CFR §26.1303, which requires documentation of ethical conduct of studies submitted after April 6, 2006, does not apply. 40 CFR §26.1602(b)(2) requires HSRB review, 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 pre-rule research if there is "clear and convincing evidence" that its conduct was fundamentally unethical or significantly deficient relative to standards prevailing when it was conducted.

The stated purpose of this research was to characterize the relative involvement of acrolein in the effects of air pollution caused by cigarette smoke. The authors concluded that acrolein was not a significant contributor to the irritancy of cigarette smoke. They reported threshold irritancy effects for pure acrolein at measured concentrations. Irritancy information shows humans to be the most sensitive species and is of potential value to EPA in defining an endpoint for assessing risk to humans from exposure to acrolein when it is used as a pesticide.

The subjects participating in this research were described only as healthy college students. Roughly equal numbers of males and females were enrolled in each of three tests (Test A: 31 males and 22 females; Test B: 17 males and 25 females; Test C: 21 males and 25 females). The report does not describe how subjects were recruited, any relationship between the investigators and the subjects; subject age and reproductive status; the sequence in which Tests A, B, and C were conducted; the time lapse between sub-studies; whether any subjects participated in more than one sub-study; or whether subjects were compensated for participating. The primary risks to subjects were eye, nose, and throat irritation from exposure to acrolein, a known strong irritant. The report does not describe the qualitative nature or likelihood of risks, the

probable duration or reversibility of effects, or any steps taken to reduce risks to the subjects. The research offered no direct benefits to subjects, but societal benefits included improved understanding of the threshold irritation effects of acrolein in humans, confirmation of the U.S. Threshold Limit Value level for 8-hour exposure, and evidence that the Occupational Safety and Health Administration (OSHA) limit for peak exposures was set too high. Based on the report, it is unclear what benefits were anticipated and insufficient information is available to assess the risk-benefit balance.

The report does not describe ethics oversight, independent ethics review, or any standard of ethical conduct. The report also does not indicate whether or how participants were informed or how their voluntary consent to participate was obtained. The privacy of the subjects was not compromised in the published report. A common subjective response measure was reported as a "wish to leave the room;" during the 60-minute continuous exposure to 0.3 ppm acrolein, 50 percent of subjects had a "wish to leave the room" after 10 minutes, rising to 72 percent after 20 minutes, but the report does not indicate whether any exposures were terminated early because of a subject's expressed wish to leave the inhalation chamber.

No prevailing standard of ethical conduct was identified in the report. The prevailing standard thus is assumed to be the Declaration of Helsinki (DoH), 1975, which prevailed in medical research in 1977, but may not have been considered applicable to this research. The basic principles of the DoH state that the design of an experimental protocol should be clearly formulated and evaluated by an independent committee; biomedical research involving human subjects cannot be performed unless the importance of the objective is in proportion to the risk to the subject; every such project should be preceded by careful assessment of predictable risks compared to foreseeable benefits to the subjects or to others; and any potential research subject must be adequately informed of the aims, anticipated benefits, and potential hazards and discomforts of the study, and should be clearly informed of their right to abstain from participation or withdraw consent to participate at any time. For non-therapeutic research, the DoH states that the subjects should be volunteers and the research should be discontinued if judged to be harmful. The interest of science and society should never take precedence over considerations related to the well-being of the subjects.

Ethical concerns indicate a lack of evidence that the protocol was evaluated by an independent committee; however, this is typical for published human studies from this time period and does not constitute "clear and convincing evidence" of failure to adhere to this regulation. The report also does not indicate whether the importance of the objective was in proportion to the inherent subject risk or whether the project was preceded by assessment of risks in comparison to benefits; again, clear and convincing evidence of deliberate failure to adhere to these regulations is lacking. Other ethical concerns based on the published report include a lack of information on recruitment and informed consent procedures and whether exposures were ended early because of a subject's wish to leave the inhalation chamber. Although the investigators were aware of new U.S. standards for occupational safety (0.1 ppm for an 8-hour total weight average [TWA] and 0.3 ppm short-term exposure limit [STEL] for up to 15 minutes at a time, up to 4 times per day). If the rate of increasing concentration in sub-study A was constant over 35 minutes from zero up to 0.6 ppm, then the concentration was greater than the 15-minute STEL for about 23 minutes out of the 40 minutes in that sub-study. In test C,

exposure for 60 minutes at 0.3 ppm was at the maximum permitted by the U.S. (4 by 15-minute a day STEL). So it was within it, but the quota for the day was consumed in that one hour.

40 CFR §26.1703 forbids EPA to rely on research involving intentional exposure of pregnant or nursing women or children; the subjects in this research were described as college students, and were thus likely to have been at least 18 years old. Roughly half the subjects were female, but the report does not indicate their reproductive or nursing status. When evidence concerning subject age and reproductive status is both absent and unobtainable, it is EPA's policy that §26.1703 does not prohibit reliance on a study. 40 CFR §26.1704 forbids EPA to rely on pre-rule research if there is "clear and convincing evidence" that its conduct was fundamentally unethical or significantly deficient relative to standards prevailing when it was conducted. Very little is known about the ethical conduct of this research, and information to clarify ethical questions is not available. However, in the absence of "clear and convincing evidence" there is no regulatory barrier to EPA's reliance on this study.

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

Dr. Philpott noted that one stated societal benefit pertained to evidence that the OSHA limits were set too high and asked whether this indicates that the current limit is too high and EPA is seeking to lower it. Mr. Carley explained that the authors concluded that the OSHA limits were too high and claimed that checking these values was a societal benefit; however, this idea may have developed after completion of the study and may not have influenced the initial analysis of risks and benefits. Dr. Philpott inquired how EPA would use information from this study. Mr. Carley responded that the information would be used as a point of departure for assessing risk to bystanders and workers of intermittent short-term inhalation exposure to acrolein. Dr. Brimijoin asked if EPA was attempting to establish a point of departure where none exists or to refine an existing point of departure value. Ms. Daison answered that using this data would result in a more protective value than those permitted by existing OSHA rules.

Dr. Sharp asked whether it was appropriate for the HSRB to consider EPA use of this material. Dr. Brimijoin questioned what EPA's response would be if the HSRB found a completed study to be scientifically excellent and indicative of grossly unprotective existing regulations, but obviously deficient relevant to applicable ethical standards. Mr. Jordan answered that current regulations allow EPA to use unethical studies to establish more stringent standards for human health protection. As part of this, the views of the HSRB must be sought and time must be provided for public comments concerning EPA reliance on potentially unethical studies. EPA must demonstrate that the information is crucial to improve public health, that changes in standards cannot be justified without using the unethical study, and must publish its discussions and findings concerning these matters. In the case of the acrolein studies, it is not clear whether use of this information would result in lowering of standards. EPA currently is

discussing appropriate uncertainty factors to use in its risk assessment and concluded that the study provided an appropriate point of departure. This combined with the uncertainty factor leads to a lower reference dose and to more stringent regulatory controls on the use of the product. This meeting fulfills EPA's requirement to obtain the views of the HSRB before use of such information.

Public Comments

Dr. Brimijoin invited oral public comment on the Weber-Tschopp et al Human Study. No oral public comments were received.

Board Discussion

Scientific Considerations—Acrolein

Dr. Lebowitz opened the scientific discussion of the acrolein studies. He stated that he was familiar with this research because in 1981, he chaired an EPA advisory committee on pollution from tobacco smoke research in which these reports were used as evidence. Dr. Lebowitz complemented OPP's review of the studies. The study measured ocular irritation objectively and also noted other signs and symptoms of exposure. Noticeable irritation occurred within seconds at 0.3 ppm. High airborne concentrations can result in increasingly severe irritation, which is an effect of acrolein's high solubility. Because of potential exposure to the general population through the atmosphere, OSHA recommends a limit of 0.1 ppm in a room. The ATSDR toxicity profile shows that comparable cellular changes in the human nasal passages and initiation of human irritation occur at the same level of acrolein exposure.

Concerning the Weber-Tschopp study, Dr. Lebowitz emphasized the careful measurement and reproducibility of the acrolein concentration within the test chamber as a strength of the study. The chamber itself was well-designed and operates in a defined manner. The chemical analysis in the report was appropriate and accurate. Healthy subjects were used, although the degree of subject overlap among the three studies is unknown. Stopping rules likely were in place and intermittent exposure was sufficient to cause acute effects and allow determination of a LOAEL. The recorded measurements—eye blink, respiratory rates—were appropriate. Dr. Lebowitz agreed with the weaknesses of the study outlined by Dr. Khasawinah. Dr. Lebowitz concluded that, in his opinion, the study contains information sufficient for assessing human risk arising from potential acute inhalation exposure to acrolein.

Dr. Lehman-Mckeeman continued the discussion by agreeing that the study does provide scientific data that can be used to determine a point of departure for acrolein risk assessment activities. Dr. Lehman-Mckeeman stated that she did not agree with EPA's assessment that humans are more sensitive than animals. The studies used different measurements; human indications of distress were subjective and it is unknown whether rats experience distress earlier than can be noted by a human observer and before histopathological lesions are evident. The numerical values derived from the data are meaningful and it is a strength that these values are consistent with current OSHA standards. Dr. Lehman-Mckeeman concluded that the data have been generated in a scientifically valid manner and can be used by EPA.

Dr. Kim stated that his conclusions were similar to those of Drs. Lebowitz and Lehman-Mckeeman. The study is reasonable and sound enough to use its data as a point of departure for EPA risk assessment activities. He noted that the studies appear to have a large sample size, but there is no justification for choosing those sample sizes. False negative rates cannot be assessed, nor can the significance of the differences in reactions noted at different concentrations of acrolein; however, a lack of significance is not a lack of effect. Dr. Kim noted that the study participants were close in age and asked whether there is any evidence indicating that human sensitivity is age-dependent. Dr. Lebowitz answered that the age of the participants (likely between 18 and 26 years) was typical for human exposure studies. He added that the authors chose exposure levels based on EPA evidence concerning ambient exposure at 3, 6, or 9 parts per billion. In the presence of tobacco smoke, indoor air concentrations of acrolein can be significantly higher than this. Dr. Lebowitz informed the Board that the researchers had received funding from a tobacco company and also that an independent review of the research had been performed.

Dr. Fish asked Dr. Lebowitz to comment on any stopping rules applicable to this research. Dr. Lebowitz remarked that the independent scientific review group always considered this issue and insisted on stopping rules for safety. The stopping rules for this study were adequate for stopping the research for indications of asthma, serious reactions, and acute morbidity. The issue of whether irritation occurred at or before the levels indicated in the study must consider cultural issues and also the year in which the study was conducted, with respect to typical exposure to tobacco smoke containing acrolein. Dr. Lebowitz added that when studies are performed outside of the United States, differences in perceptions of risk and whether applicable rules were sufficient must be considered.

Dr. Brimijoin summarized by thanking Dr. Lebowitz for his insights into the science and the investigators who performed this research. The work was considered to be innovative and of high quality, with a strong study design and validation of test concentrations. The study was well-controlled and gave reliable and usable results. Dr. Lehman-Mckeeman concurred with Dr. Lebowitz and observed that humans and animals likely have similar sensitivity to acrolein. Dr. Kim also agreed, but noted that the statistical analysis used had no justification for sample size; thus the low end of the effects cannot be accurately determined. There was strong consensus among Board members that the study was scientifically reliable.

Ethical Considerations—Acrolein

Dr. Fish opened the ethics assessment by noting that there is much that is unknown about this study. The number of individual subjects used could range from 56 to 141 and how many may have participated in more than one test is unknown. There also is little information about the subjects themselves; whether any were students or employees of the investigators; how they were recruited; and what they were told about risks, their freedom to withdraw, or the informed consent process. The description of expressing a “wish” to leave is problematic because it does not necessarily indicate that a subject would leave; a subject may have “wished” to leave but did not actually leave. There is no information concerning compensation, possible undue influence, or the applicable version of the DoH. Dr. Lebowitz stated that the study was reviewed

independently for science, but did not indicate whether an independent ethics assessment had been performed. There was no justification for the sample size, which raised questions as to whether more subjects than necessary were placed at risk. Another issue concerns whether the study should have been stopped when indications of a wish to leave (after 10 and 20 minutes) became evident. The subjects were tested in groups of three and it is unclear whether the investigators analyzed the data as it was obtained to determine irritation levels or if the analysis was not performed until all subjects had been tested. Thus, it is unknown whether the study should have been stopped sooner, as accumulating evidence suggested irritation was occurring. Despite this, Dr. Fish indicated that she agreed that stopping rules for subject safety likely were in place. Dr. Fish concluded that there is not clear and convincing evidence that the studies were unethical or deficient relative to existing standards.

Dr. Sharp stated that review of this research was challenging because of the lack of documentation. He noted that there was no clear evidence that vulnerable subjects were adequately protected and appropriately recruited, but this is not grounds for concluding that the study did not comply with existing standards. Concerning the ability to opt out of a study, it is disconcerting to note that 72 percent of subjects expressed a wish to leave the chamber at 20 minutes but did not withdraw from the study. A further explanation of this would be helpful, but does not indicate that the study was not compatible with existing standards. Statements concerning independent review by external advisory panels generally were not included in publications in 1975, thus, the lack of this information in the manuscript is not evidence that such a review did not take place.

Dr. Sharp said that the study was significantly deficient relative to prevailing ethical standards, particularly DoH Part I-9. This standard calls for evaluation of the importance of the objective relative to subject risk. In this work, acrolein was characterized as “highly toxic” and there was no intent of the research to provide therapeutic benefit or diagnostic results, and no benefit at all to the subjects. Intentional exposure to this highly toxic substance thus constituted an inappropriate risk-to-benefit ratio.

Dr. Philpott commented that he was less sure of the ethics of this study than Dr. Fish, but not as concerned as Dr. Sharp. Part I-9 of the DoH is a topic of significant debate concerning its exact meaning. The importance of the objective relative to subject benefit is subjective. Dr. Philpott’s main concern was with the informed consent process; the way EPA’s human studies rule is written with respect to completed studies is complicated. Dr. Philpott agreed with Dr. Fish that there was no clear and convincing evidence that the study was significantly unethical or deficient relative to existing standards. He would strongly recommend to EPA as they decide whether or not to use this information that they carefully consider whether use of this information would lead to more protective standards and consider whether the information from the animal studies would suffice for its risk assessment work.

Dr. Lebowitz clarified that any information he provided on the laboratory, its investigators, informed consent, compensation, or recruitment was based largely on hearsay. He was not a reviewer of this particular study. He noted that he reviewed later studies with similar designs, but these reviews did not include a thorough ethical review as performed by the HSRB. His statement concerning independent review was factual. Concerning the number of students,

Dr. Lebowitz noted speculation on overlap of subjects among studies was based on information he had been provided with in previous reviews but is not in EPA's documents. He also added that stopping rules were always required by the sponsors of this research and the university at which the research was performed.

Dr. Chadwick expressed his discomfort with reviewing a study for which significant information is lacking. The Board does not know when the study was performed and thus does not know which version of the DoH applies; the 1964 DoH was significantly revised in 1975. The DoH was written by physicians with them as its primary target, thus the document may not apply to non-medical facilities. Dr. Kim clarified that the stopping rule referred to safety of the subjects, and asked whether "stopping" meant the study stopped or the subjects left the chamber. Dr. Lebowitz remarked that the investigation of that particular subject was stopped, but the study itself did not come to an end. He added that Weber was the primary investigator who observed the subjects at all times. In response to a question from Mr. Carley, Dr. Lebowitz clarified that none of the investigators were medical doctors, but medical doctors participated in the review and screening of subjects for similar studies, although he could not state definitively whether such screening was performed for this study.

Dr. Fish asked the Board to discuss the meaning of "highly toxic" as related to acrolein exposures that took place in this study. Dr. Lebowitz said that higher airborne concentrations (between 2 and 5 ppm) result in increasing irritation over the entire respiratory tract. Relative to this, the doses used in this study were not considered highly toxic. Dr. Lehman-Mckeeman noted that acrolein is an aldehyde and a reactive moiety that can do damage at the point of contact; because of this, there are minimal systemic effects associated with acrolein. Evidence of this is in the animal studies, in which inhalation resulted in damage primarily to the respiratory system (changes in adrenal gland weight likely were due to the stress of the experiments). She summarized that acrolein is highly irritating, has an odor threshold, and manifests toxicity at the point of contact. Dr. Brimijoin asked Dr. Sharp to comment on his statement that the study is significantly deficient with respect to ethical standards of the time because of the failure of the study's objectives to justify subject risk. Dr. Sharp remarked that his view had not changed; acrolein may not cause systemic damage, but the harm posed to the subjects by irritation is not offset by the purported societal benefit. Dr. Philpott commented that the timing of OSHA regulations regarding acrolein exposure and the demands of DoH on such experiments should be considered in the Board's ethics assessment. He added that Board members appeared to have different opinions concerning the ethics of this research, and perhaps should strongly suggest to EPA that the Agency's decision on whether or not to use this data rest on whether the information will result in significantly increased protection. Dr. Menikoff reminded Board members that it is inappropriate to conclude that there is clear and convincing evidence that the work was unethical or did not meet the relevant standards of the time if documentation was not available.

Dr. Brimijoin summarized that several Board members believed that the study was not fundamentally unethical nor was it significantly deficient. Dr. Sharp believed the study to be fundamentally unethical because of an inappropriate risk-to-benefit balance. Dr. Chadwick raised questions concerning whether the DoH would apply to this work, and if not, what impact this would have on the views of Board members who believe the study to be ethical. If the net

effect of using this information is to increase human protection, EPA has mechanisms in place to permit it to use the data.

Dr. Richard Fenske said that the DoH likely was the prevailing standard at the time, and it is difficult to believe that the study did not include medical supervision because it did involve humans; there was likely to have been some degree of oversight from the medical community. Mr. Carley acknowledged that application of DoH Part I.4 required a judgment call, driven by the available facts. He suggested to Dr. Sharp that it would be helpful if Dr. Sharp could identify the available evidence that led him to conclude that the provisions of Part I.4 were not met. Dr. Sharp answered that the definition of acrolein as highly irritating and known to be toxic at high concentrations was not outweighed by any of the societal benefits documented in this report.

Dr. Lebowitz explained that information from this study was applicable and considered during development of the Clean Air Act. Data from this and similar research was instrumental in developing tobacco smoke exposure regulations and laws that banned tobacco smoke in many places. The societal benefits of these activities, in the forms of occupational and societal regulations and worker protection standards, have been substantial by reducing tobacco smoke exposure to many people. This and other studies were considered scientifically sufficient given the standards of the time to justify placing regulations on tobacco smoke. Dr. Sharp remarked that assessing the benefits of what are post-hoc results is complicated. He was not convinced that at the time the study was conducted, such benefits clearly outweighed subject risk. Dr. Brimijoin concluded that the Board's report would indicate that although a majority of members did not find the research to be significantly ethically deficient, at least one Board member disagreed with this assessment.

EPA Science and Ethics Assessments of Three Published Clinical Studies on 4-Aminopyridine (4-AP)

Introduction

Mr. Carley presented background information on three clinical studies of 4-AP. 4-AP is a chemical intermediate in the production of certain pharmaceuticals and agrochemicals. It has been used as an experimental drug for treatment of spinal cord injury (SCI), multiple sclerosis (MS), and has orphan drug status for treatment of Guillain-Barre Syndrome. 4-AP is a fast potassium channel blocker, improves axonal conduction in demyelinated nerve fibers and is an antagonist to non-depolarizing neuromuscular blocking agents. 4-AP also has pesticidal use as a bird repellent (Avitrol).

Three 4-AP clinical studies were considered in this review, including the following:

1. Van Diemen, H., et al. (1993) 4-Aminopyridine in Patients with Multiple Sclerosis: Dosage and Serum Level Related to Efficacy and Safety. *Clinical Neuropharmacology* vol. 16 No. 3, pp. 195-204. MRID 47093603.

2. Segal, J., et al. (1999) Safety and Efficacy of 4-Aminopyridine in Humans with Spinal Cord Injury: A Long-Term, Controlled Trial. *Pharmacotherapy* 19(6):713-723, 1999. MRID 47093602.

3. Grijalva, I., et al. (2003) Efficacy and Safety of 4-Aminopyridine in Patients With Long-Term Spinal Cord Injury: A Randomized, Double-Blind, Placebo-Controlled Trial. *Pharmacotherapy* 23(7):823-834. MRID 47093601.

The study by Van Diemen et al was conducted at the Free University Hospital in Amsterdam in the early 1990s. It was a randomized, placebo-controlled, double-blind crossover study involving 70 patients with MS. 4-AP was administered by both oral and intravenous (IV) routes. The authors had previously reported a possible therapeutic effect of 4-AP on patients with MS; this paper reports the relationship between dosage, serum level, efficacy, and side effects of 4-AP in the same patients. The study by Segal et al was conducted at the Veterans Administration (VA) Medical Center in Long Beach, CA, in the late 1990s. This medical center had a registered IRB and holds a FWA from OHRP. The study was a randomized, active-treatment-controlled, partially-blinded trial performed on 21 adult outpatients with traumatic SCI of at least 2 years' duration. 4-AP was orally administered. The article reports improvements in the patients' condition with no significant associated drug toxicity, and thus indicates thresholds for side effects useful to EPA in assessing hazard. The study by Grijalva et al was conducted in 1999-2000 at the Instituto Mexicano del Seguro Social (IMSS) in Mexico City. It was a randomized, placebo-controlled, double-blind crossover study in 27 adult outpatients with traumatic SCI of at least 1.5 years' duration. 4-AP was orally administered and this report also details improvement in patients' condition with no significant associated toxicity.

Scientific Considerations

Dr. Khasawinah presented the science assessment of the three trials. 4-AP is soluble in water and in organic solvents. It is highly toxic with an LD50 of 3.7 to 20 mg/kg. Accidental ingestion of approximately 60 mg (0.86 mg/kg for a 70-kg adult) of 4-AP resulted in rapid onset of symptoms such as weakness, dizziness, dyspnea, profound thirst, and combative behavior.

The Van Diemen et al study enrolled 43 women and 37 men with MS, between the ages of 23 and 68 years. Phase 1 of the study involved IV administration of 1mg 4-AP in 1 to 2 minutes over 20 minutes for the first 4 hours and then 2.5 mg in 1 to 2 minutes for 20 minutes afterward, to a maximum dose of 0.5 mg/kg. The infusion duration was 60 to 260 minutes. Phase II involved oral dosing of 4-AP as nonenteric-coated capsules or placebo for 12 weeks, beginning 1 week after Phase I. Dosing started at 10 to 20 mg/day in 2 to 4 divided doses, increasing by 5 to 15 mg/day at week 2 and 6 (or week 14 and 18) to a maximum of 0.5 mg/kg/day.

Serum levels of 4-AP were measured in subjects who received IV infusions. The mean level 80 minutes after beginning infusion was 38.1 nanograms (ng) per milliliter (mL) (range = 24 to 45 ng/mL), 63.4 ng/ml at the end of the infusion (range = 26 to 86 ng/mL), and 36.6 ng/mL 120 minutes after the end of the infusion (range = 22 to 58 ng/mL). Side effects included paresthesis in the infusion arm (observed at a minimum dose of 1 mg), perioral paresthesis

(1 mg), dizziness and light-headedness (9 mgs), dizziness/lightheadedness and nausea/vomiting (10 mgs), dizziness/light-headedness and a feeling of restlessness (9 mgs), and headache (20 mgs). All side effects were reversed within 2 hours after cessation of infusion; seven patients reported no side effects.

The oral phase of 4-AP administration resulted in a mean dosage of 31.2 mg per day (mg/day) (range of 10 to 50 mg/day; 0.17 to 0.55 mg/kg/day) in 2 to 4 doses. Average 4-AP serum levels were 53.6 ng/mL (range of 7 to 107 ng/mL) and increased 1.3 ng/mL/mg per day. Side effects included paresthesias/dysesthesias in 15 patients at a minimum oral dose of 5 mg/day; dizziness/light-headedness in 36 patients at 5 mg/day; gait instability in 11 patients at 5 mg/day; nausea or vomiting in nine patients at 5 mg/day; restlessness/anxiety in four patients at 5 mg/day; abdominal pain in five patients at 10 mg/day; and obstipation in one patient at 25 mg/day. Side effects were reported after 30 to 45 minutes and resolved within 2 to 5 hours of 4-AP administration. Fourteen patients required dose reduction and three withdrew due to side effects. No side effects were reported by 15 patients, but one had significant electroencephalography (EEG) changes. More pronounced side effects were observed if the oral 4-AP was administered when the subject had an empty stomach. The authors concluded that the patients showed statistically significant improvement in smooth pursuit gait when receiving 4-AP by either through IV or oral administration. Improvement was proportional to 4-AP serum level, with serum levels of 60 ng/mL and above providing the best results. The minimum oral LOAEL was established as 5 mg/day.

The Segal et al study was a randomized, open label, dosage blinded trial with active-treatment-control. It enrolled 21 patients with SCI of at least 2 years (14 tetraplegic and seven paraplegic). 4-AP dosages were administered in increments of 2, 5, or 10 mg for 2 weeks as immediate release encapsulated 4-AP. Patients were divided into three groups. Group A had six patients who were dosage-blinded and 4-AP naïve; dosage was titrated to 30 mg/day for 3 months. Group B consisted of five dosage-blinded, 4-AP naïve patients who received 6 mg/day in divided doses for 3 months. Group C had 10 patients who were dosage-cognizant, had received 4-AP for more than 1 year before the study, and received 30 mg/day for 3 months during this study.

Segal et al reported no clinically significant adverse effects. Side effects included nervousness, giddiness or dizziness, and gastrointestinal upset as mild abdominal cramps or nausea. Side effects were transient, self-limited, or disappeared with changes in dosage or timing of drug ingestion with meals. Some patients reported enhanced mood. No seizure or seizure-like activity was observed or reported by patients or caregivers at any time or at any dosage. Serially acquired EEG, electrocardiogram, biochemical and hematologic profiles, and urinalyses remained within normal ranges. Clinically meaningful improvements (as defined by American Thoracic Society criteria) were seen at 1 month, and persisted at 3 months in subjects receiving 4-AP at 30 mg/day compared to the low-dose control group receiving 6 mg/day. The authors concluded that 4-AP is a potentially toxic drug with a narrow therapeutic index, but significant toxicities were not observed, probably because of careful patient selection and individualized dosing regimens. This work established a LOAEL of 5 to 10 mg/day.

The study performed by Grijalva et al enrolled 27 patients with long-term SCI. Patients received 4-AP by oral dose of 5 mg/day, which was increased by 5 mg/week to a maximum dose of 30 mg/day; 2 capsules were given every 8 hours for a total of 6 capsules/day over 12 weeks. Patients were divided into two groups. Group A received 4-AP for 12 weeks while Group B received placebo; the groups switched after 12 weeks.

A complete safety evaluation was performed every 4 weeks. Two patients withdrew from Group A, for reasons unrelated to 4-AP. One patient in Group B had a moderate adverse reaction (arterial vasospasm). Reported adverse reactions included dry mouth (dosage range of 5 to 30 mg/day); dizziness (5 to 30 mg/day); nausea (15 to 30 mg/day); gastritis (10 to 30 mg/day); paresthesia (30 mg/day); arterial vasospasm (20 mg/day); side effects included insomnia, anxiety, headache, cramps, memory alterations, increased saliva viscosity, bitter taste in mouth, and global pinching pain (5 to 30 mg/day). These side effects (except for arterial vasospasm) were also observed in patients receiving placebo. Diaphoresis, abdominal distention, abdominal pain, phosphenes, hyperphagia, and itchy eyes also were reported by seven patients who received placebo and none of the patients receiving 4-AP. There was some confusion about interpretation of side effects data concerning whether the effects were noted in patients receiving placebo before or after they received 4-AP. Adverse reactions occurred within the first week of receiving 4-AP and usually resolved within 1 to 2 hours. Some mild signs of liver effects were observed but resolved during or shortly after discontinuation of treatment.

The authors concluded that 4-AP was beneficial and provided positive gains in motor function, sensation, and independence; these effects were observed in more patients (69 percent) receiving 4-AP than patients receiving placebo. The authors also state that patients should be monitored for peripheral vasospasm. This work sets a LOAEL for adverse effects of 5 mg/kg.

EPA's summary assessment of these studies found that 4-AP serum levels were proportional to dose, short-lived, and declined after exposure termination. There is a therapeutic value of 4-AP associated with its continued use. All adverse effects occurred after 4-AP intake and were proportional to dose. The three studies are complimentary; Girjalva et al is the most detailed and Van Diemen et al provides important information on serum 4-AP levels. The studies helped EPA determine a minimal LOAEL for short- to long-term exposures of 5 mg/day, equivalent to 0.07 mg/kg/day.

Dr. Brimijoin asked Dr. Khasawinah if he had noted any deficiencies or questionable aspects of these studies from a scientific perspective. Dr. Khasawinah answered that the studies were well-controlled and the patients were closely monitored. The reported adverse effects may have been an underestimation of the true adverse effects, which could lead EPA to underestimate risks associated with 4-AP. When birds eat corn treated with 4-AP, they show severe reactions. EPA would use the LOAEL from this assessment as a baseline for risk assessment.

Dr. Lebowitz asked how the adverse effects were used to determine the LOAEL. Dr. Khasawinah explained that the minimal dose that produced any effect was used. Dr. Fenske noted that the weight of evidence document stated that there was no data on acute, sub-chronic, oral, or inhalation toxicity, no information on developmental or reproductive toxicity and no information on potential carcinogenicity. He asked how, if this is true, this product could be

registered. Mr. Jordan explained that EPA data requirements depend on the use pattern of a product. For a product that may get into the food supply, very extensive data are required. If the use pattern indicates that human exposure opportunities will be limited, fewer toxicity studies are required. The 4-AP use pattern indicates that humans are not likely to be exposed through food, water, or most work practices, therefore, less data were needed. 4-AP also is an older product that was registered years ago at a time of less demanding data requirements and thus has limited toxicity data. For the purposes of current risk assessment activities, EPA is attempting to find the best data available to permit ongoing use of 4-AP as described by current regulations.

Dr. Fitzpatrick asked why 4-AP was not anticipated to enter the food supply if it was used on crops or could be accidentally ingested by animals. Mr. Jordan explained that it is unknown whether 4-AP sprayed on crops is taken up by the plants. Mr. Ray Kent (OPP, EPA) commented that this has been an issue in the past because 4-AP-treated corn designed to keep birds away from crops was distributed throughout the fields and could lodge in growing corn, but because of differences in 4-AP distribution, this is no longer an issue. Mr. Jordan noted that because of potential risk to non-target species, EPA required separate studies of 4-AP on different bird species and fish to evaluate differences in effect.

Ethical Considerations

Mr. Carley provided EPA's ethics assessment of the three studies. All three articles were considered in EPA's ethics review on May 22 and 25, 2007. The articles were reports of research involving intentional exposure of human subjects in clinical trials of experimental pharmaceuticals. All three studies pre-date EPA's rule. Two (Segal and Grijalva) were subject to the Common Rule, the third (Van Diemen) to the rules in place in the Netherlands in 1993. The research was not conducted with the intention to submit it to EPA under the pesticide laws and was not submitted by a regulated entity; instead, EPA retrieved the articles from the published literature. Since the documents were not submitted to EPA, 40 CFR §26.1303, which requires documentation of ethical conduct of studies submitted after April 6, 2006, does not apply. 40 CFR §26.1602(b)(2) requires HSRB review. 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 pre-rule research if there is "clear and convincing evidence" that its conduct was fundamentally unethical or significantly deficient relative to standards prevailing when the research was conducted.

The Van Diemen article reports the relationship between dosage, serum level, efficacy, and side effects of 4-AP in 70 patients with MS participating in a drug trial. This information is of potential value to EPA in defining endpoints for assessing risk to humans from exposure to 4-AP when it is used as a pesticide.

Subjects included in the Van Diemen trial were 43 women and 37 men with MS for periods from 2 months to 25 years, ages 23 to 68 years. The subjects did not have hepatic or renal disease or any history of epilepsy. The reproductive or nursing status of the women was not reported, nor was the means by which subjects were recruited. All 70 subjects participated in the first (IV) phase of the research; one did not participate in the second (oral) phase for reasons unrelated to this study. Risks to subjects included potential serious side effects reported in

earlier studies of clinical use of 4-AP to treat MS. This study used a rising-dose design and close monitoring to explore the relationship between dosage, serum level, efficacy, and safety of 4-AP used to treat patients with MS. All subjective side effects were registered; as they increased, dosing was lowered or discontinued. All side effects were monitored to resolution and blood chemistry was extensively monitored, as were cardiac, hepatic, and renal function.

Concerning the benefits of this research, the efficacy measures described in this article implied that the research offered therapeutic benefits to subjects. Societal benefits include further insights into potentially effective treatment of MS and improved understanding of thresholds for side effects of 4-AP, including pain, paresthesia, dizziness, headache, gait instability, nausea, restlessness/anxiety, abdominal pain, and obstipation. The information provided in this study suggests that benefits were sufficient to justify the risks to individual subjects.

The Van Diemen protocol was approved by the Ethical Committee of the Free University Hospital, Amsterdam, but the report identifies no prevailing standard of ethical conduct. The DoH (1989) was assumed to be the relevant standard, and there is no indication that conduct of the study was deficient relative to DoH standards. Informed consent was obtained from all patients before they were accepted into the study; no further details are provided. The privacy of subjects was not compromised in the published report.

The purpose of the Segal study was to determine the effects of long-term administration of 4-AP on sensorimotor function in humans with long-standing SCI. The article reported improvements in the patients' condition with some minor side effects but no significant associated drug toxicity. This information is of potential value to EPA in defining endpoints for assessing risk to humans from exposure to 4-AP when it is used as a pesticide.

Subjects included 18 men and 3 women with traumatic SCI of at least 2 years' duration. Ten subjects had previously been exposed to 4-AP in a short-term test; the remaining 11 had never been exposed to 4-AP. One additional subject began the study but did not complete it for reasons unrelated to the study. Pregnant women were excluded, but the means by which subjects were recruited were not reported. Concerning risks to subjects, previous studies had shown that 4-AP in the dose range administered could be effective in treating SCI with relatively few side effects. The subjects were extensively monitored before initiation of treatment and at intervals during the research. Although the study was conducted on an outpatient basis, investigators maintained daily telephone contact with subjects. All side effects were monitored to resolution.

Efficacy measures demonstrated that the research offered therapeutic benefits to subjects. Societal benefits include further insights into potentially effective treatment of SCI and improved understanding of thresholds for side effects of 4-AP. The information available suggests that the benefits were sufficient to justify the risks to individual subjects.

Concerning independent ethics review, all subjects "provided institution-approved, written informed consent," and the report identified no standard of ethical conduct. The VA hospital at which the research was conducted had a registered IRB, held a FWA from OHRP, and is subject to the VA Common Rule. Informed consent was obtained from all patients, but no

further details were provided. The privacy of subjects was not compromised in the published report. The prevailing standard of ethical conduct was the Common Rule and 21 CFR Parts 50 and 56; there is no indication that conduct was deficient relative to these standards.

The purpose of the Grijalva study was to examine the efficacy and safety of 4-AP and to document sensorimotor changes after discontinuation of the drug in patients with long-term SCI. The article reports improvements in the patients' condition with some minor side effects but no significant associated drug toxicity. This information is of potential value to EPA in defining endpoints for assessing risk to humans from exposure to 4-AP when it is used as a pesticide.

Twenty-one men and 4 women, ages 23 to 48 years, with traumatic SCI of at least 1.5 years' duration completed the study; two others withdrew for reasons unrelated to the study and three withdrew late in the study, but their data were included. Before enrolling, each participant underwent a comprehensive clinical evaluation. Pregnant or nursing women were excluded but the means by which subjects were recruited were not reported.

Previous studies had shown that 4-AP in the dose range administered could be effective in treating SCI with relatively few side effects. The subjects were extensively tested before initiation of treatment and at intervals during the research. All but one of the side effects reported were mild, but some effects not previously reported were noted. All side effects were monitored to resolution.

As with the other two studies, potential benefits include efficacy measures that demonstrated potential therapeutic benefits to subjects. Societal benefits included increased information on a potentially effective treatment for SCI and improved understanding of the threshold for side effects associated with 4-AP use. The information provided by Grijalva et al suggested that the benefits of the study justified the risks to individual subjects.

This research was initiated after acceptance by both the local research committee of the hospital and the National Research Council of the IMSS. The IMSS has an IRB (#3566) registered with OHRP, and holds a FWA (#4956). No standard of ethical conduct was cited in the article. Concerning informed consent, patients were fully informed in writing and verbally, and provided signed consent; no further details were reported. The privacy of subjects was not compromised in the published report. The prevailing standard of ethical conduct for this study was the Common Rule; ethical conduct was more completely reported than in most published studies and there were no indications that conduct was deficient relative to applicable standards.

EPA had reached the following conclusions based on the Agency's review of the three clinical trials of 4-AP. 40 CFR §26.1703 forbids EPA to rely on research involving intentional exposure of pregnant or nursing women or children. To this end, all subjects in the three studies were over 18 years of age, pregnant women were excluded from all studies, and nursing women were excluded from the Grijalva study. When evidence concerning subject age and reproductive status is both absent and unobtainable, it is EPA's policy that §26.1703 does not prohibit reliance on a study.

40 CFR §26.1704 forbids EPA to rely on pre-rule research if there is "clear and convincing evidence" that its conduct was fundamentally unethical or significantly deficient relative to standards prevailing when it was conducted. Despite minor gaps in documentation of ethical conduct for all three studies, there are no indications that any of the studies failed to meet applicable standards of ethical conduct. Thus, there is no regulatory barrier to EPA's reliance on these studies.

Dr. Menikoff noted that in the event of a lack of information, the Board has assumed that previously conducted studies were conducted ethically and asked if this was the accepted approach. He also asked if additional data, such as protocols or ICFs could be obtained. Mr. Carley responded that if nothing in the published reports suggest a serious deficiency, it is appropriate to accept the reports at face value. In this case, Mr. Carley did not believe there were any questions that warranted contacting the authors.

Public Comments

Dr. Brimijoin invited oral public comment on the three published clinical studies on 4-AP. No oral public comments were received.

Board Discussion

Scientific Considerations—4-AP

Dr. Brimijoin opened discussion of scientific considerations for EPA's use of the data from these studies to derive a point of departure for estimating risk to humans from exposure to 4-AP. He noted that 4-AP is a fast potassium channel blocker, which leads to a prolonged activation potential, increased nerve transduction, and increased neurotransmitter release at a wider range of terminal types. 4-AP also does not over-stimulate receptors. Concerning the scientific strengths for use of this data as a point of departure for estimating human risk from 4-AP exposure, there are advantages and disadvantages to using clinical trials data rather than animal studies to assess exposure. The weight of evidence document showed that extensive animal data exists; however, this data was not collected in a way that would help EPA determine low-level doses associated with low or no side effects. Thus, a need for more and better data exists.

Because the goals of these studies were to demonstrate a clinical effect and analyze safety with respect to therapeutic dose, they were not designed to determine the minimal amount of 4-AP that produces an effect. This presents a weakness for using the data to determine LOAEL. Dr. Brimijoin noted that the studies appear to have varying degrees of quality as clinical trials, but fail to demonstrate more than a very small, questionable therapeutic effect. The studies have major weaknesses in design and outcomes. The Segal et al study is not placebo-controlled, only dose-blinded. Powerful placebo effects were observed in this study with respect to side effects. Because of this, it is difficult to determine effects attributable to 4-AP itself. Dr. Brimijoin continued by noting that the data in the Grijalva study are confusing. The report states that adverse effects were reported by 56 percent of treated patients. Based on the number of adverse effects reported, he assumed that the effects listed in the placebo arm were occurring during

placebo treatment, but instead appear to refer to events that occurred while a patient previously treated with 4-AP was receiving placebo. Dr. Kim explained that data on adverse effects were collected over the entire course of the study, which included both a treatment phase and a placebo phase. Some patients received treatment first and then placebo, others first received placebo, followed by treatment. He noted that it does not appear that adverse effects occurred during treatment with placebo, but the report does not specifically state when the adverse effects occurred.

Dr. Brimijoin summarized that the Grijalva report is unclear concerning which adverse effects were treatment-related. The study cannot be used to establish the level of 4-AP dose at which effects were noticed because of the unclear study design and report. The Segal report focused on treatment-related effects. This report noticed nervousness, giddiness, dizziness, and gastrointestinal upset as the most frequent side effects, but these effects were not linked to the 4-AP dose level. The data from this report seem to indicate that the drug is clinically safe within certain narrow limits, but provide weak evidence upon which to base conclusions about a reference dose. The Van Diemen study does contain information that would tend to support EPA's conclusion that a LOAEL can be derived. The study was blinded and contained good detail about treatment-related side effects. The report does not establish a dosage low enough to be used to establish a no observed adverse effect level (NOAEL). A total oral dose of 5 mg/day was associated with mild but definite discomfort, but no associated blood chemistry changes. This study alone or in the context of the other studies provides information on dose that could be used to establish a LOAEL of approximately 0.07 mg/kg as a reference dose.

Dr. Fitzpatrick continued the scientific discussion. The scientific question asked by these studies concerned clinical endpoint, not safety. Existing data on 4-AP was sparse, but animal data could be used to determine dose. 4-AP is an acute neurotoxicant and the reported side effects address this. None of the three studies contain justification for dosing; this has implications for consent, particularly for the patients who received three-quarters of the previously reported toxic dose of 60 mg. Dr. Fitzpatrick noted that the patients participating in these studies could be considered members of a vulnerable population, because there are no other potential treatments for their conditions. Additionally, they may not have recognized that the trials were not designed to benefit them directly. The results of this study also are not likely to be generalizable to the general population.

All three studies focused on subjective clinical endpoints. Additionally, patients with too many side effects could be excluded from the trial, which could underestimate side effects. The investigators claim that the side effects are minor, which may be the perception of a population with few other options for treatment, but perhaps not of a healthy population. A lack of individual subject data for assessment of toxicity also is a weakness. It is difficult to conclude that all three studies could be used to establish a true LOAEL. In addition, this data would give an oral (or IV) LOAEL and it is unlikely that this is how the general public would be exposed to 4-AP.

Dr. Fitzpatrick expressed some surprise that the Segal study, conducted under the auspices of the Food and Drug Administration (FDA), received an Investigational New Drug designation with so little animal or human data. She questioned whether FDA truly supervised

the study or whether Segal perhaps had additional information that was not reported in the article. She also clarified that "orphan drug status" means that the drug is used on less than 100,000 people per year but has no implications for efficacy. She concluded that it would be difficult to support use of this data for establishing a LOAEL.

Dr. Fenske reiterated that it is important to understand that these studies were conducted to evaluate efficacy. Regarding safety, it appears that the subjects might be willing to endure strong side effects in hope of a treatment or cure for their conditions. The Segal study used different doses, and it is difficult to conclude whether the higher dose was associated with stronger side effects. The Grijalva study used the lowest dose (5 mg/day) but nonetheless reported adverse effects. This report does not clearly describe the number of patients who experienced side effects, or whether some experienced more than one, and does not indicate which side effects occurred at which dose level. In the Van Diemen study, side effects were observed in patients receiving 4-AP both orally and by IV administration. Side effects were observed in those receiving the minimum dose of 5 mg and some patients may have experienced multiple side effects. Giddiness, dizziness, and nausea are symptoms of central nervous system toxicity. Dr. Fenske stated that he would support EPA's use of the data as a point of departure for risk assessment scenarios, but would be reluctant to endorse 5 mg/day as a LOAEL, given that side effects were observed at this dose and given the steep dose-response relationship observed for 4-AP.

Dr. Kim noted that each study had flaws, particularly with reporting adverse effects. He also was concerned that the risk-benefit ratio may be different in patients compared to healthy volunteers. He took issue with non-reporting of toxicity for adverse effects treatment. The agents were used in a FDA setting, which may have different assessments of risk based on the severity of the disease the study attempts to treat. He agreed that the nature of safety data reporting was casual and not rigorously defined. He also noted that it is always difficult to confirm that improvement is related to therapy. It also will be difficult to determine whether EPA applied appropriate uncertainty factors because of differences in the risk-benefit ratio for patients versus healthy volunteers.

Dr. Lehman-Mckeeman stated that she had reservations about the overall utility of the data. In this case with actual evidence of exposure, it is ironic that EPA may not be able to use this data. She agreed that it is difficult to use these studies to assess toxicity because their primary objective was demonstrating efficacy. Dr. Lehman-Mckeeman also expressed concern with the toxicity data with respect to whether patients with SCI or MS accurately reflect events that would occur in a normal population. She said that she was inclined to think that this is an unusual subpopulation, which could relate to the perceived under-reporting of adverse effects.

Other confusing aspects of these reports include the low effect level based on total daily dosage. The daily dose was stated as 5 mg/day, but the drug was administered two to four times per day, and it is unclear whether adverse effects were observed after administration of the first, second, third, or fourth dose. Patients in the Grijalva report appeared to need several weeks of treatment before an effect was observed; these subjects received lower doses at repeated points during the day. Dr. Brimijoin agreed that this was an important observation, given the short half-life of 4-AP.

Dr. Lehman-Mckeeman continued assessment of the Grijalva report. This study reported adverse effects during the wash-in placebo period. The report appeared to indicate that 14 of 21 patients experienced 26 possible reactions, and this included effects experienced both during treatment with 4-AP and during the placebo phase. This would make it impossible to determine adverse reactions specifically related to 4-AP treatment. Information from a data and safety monitoring board or analysis of the raw data would be necessary to determine when side effects occurred. Dr. Kim noted that most reports of this type are conservative with respect to reporting treatment-emergent adverse effects and the Grijalva report described all events that occurred over the entire 26 weeks of the trial. Because of this, adverse effects may actually be over-reported.

Dr. Brimijoin summarized that much of the Board's criticism focused on the issue of the studies' value as a record of toxicity level and safe doses. This arises primarily because these studies were not designed to test for a toxic endpoint but rather to determine if 4-AP has a therapeutic effect at a safe level (accompanied only by mild toxicity). There was confusion related to the Girjalva report concerning the dose associated with treatment-induced toxicity and whether there was clear evidence of difference in toxicity between the treatment and placebo arms. Additionally, subjective side effects may have been under-reported because of a highly motivated subject population seeking treatment options for serious conditions (SCI and MS).

4-AP also has a steep dose-response curve, which could mean that doses quickly become toxic as they rise. The collective data from the studies indicate that a dose of between 5 and 10 mg/day is not associated with dramatic toxicity. EPA would like to call this dose the LOAEL and use it as a point of departure. Several Board members have spoken against specifically relying on this data for a point of departure. Although Dr. Brimijoin stated that he initially believed 5 mg/day would be a defensible point of departure, after hearing discussion from other Board members he now would not enthusiastically endorse this.

Dr. Fenske stated that the science was sound and the studies well conducted. The side effect reporting was not systematic. If EPA believes it is important to use this data to establish a LOAEL, Dr. Fenske would not prevent it, but neither would he strongly endorse doing so.

Dr. Kim inquired whether EPA had other resources to use to establish a LOAEL for 4-AP. Dr. Khasawinah responded that there is little data from the literature upon which to rely, which is why all three studies were presented; EPA believed the three would complement each other. He stated that taken together, the studies seem to indicate that 5 mg/day would be an acceptable LOAEL and EPA also can include uncertainty factors for more protection. EPA traditionally includes a 10-fold uncertainty factor but could increase this for this case. Dr. Lebowitz disagreed about the lack of data on 4-AP, describing other clinical trials that used a sustained-release form of the drug and suggested that EPA may wish to analyze these studies to gain more clarity on this issue, given the Board's reluctance to endorse use of the three studies presented at this meeting. Dr. Brimijoin commented that peak serum levels would be different for a sustained-release form of 4-AP. Dr. Fenske noted that the weight of evidence documents referred to animal studies that determined a LOAEL of 3 ppm and asked if EPA could use these studies. Dr. Khasawinah explained that these studies had limited information. Dr. Fenske asked

why human data was needed if a NOAEL was available from animal studies. Dr. Khasawinah replied that the animal studies were not considered acceptable. He added that the studies using the sustained release form of 4-AP also measured efficacy and reported side effects in a manner similar to that used by the three studies presented at this meeting.

Dr. Brimijoin stated that 5 mg/day probably was in the correct range for a LOAEL, but the design and reporting of the studies does not allow the Board to conclude this with a high level of confidence. He endorsed EPA's consideration of this data with some reluctance. Because of the uncertainty of the data, EPA should treat the Board's approval as provisional and should incorporate uncertainty factors in its development of a reference dose for 4-AP.

Ethical Considerations—4-AP

Dr. Menikoff opened the ethics discussion. He stated that because these are completed studies, the Board is restricted in its analysis and must assume, in the absence of clear and convincing evidence of unethical conduct, that the studies were ethically conducted. He agreed with Mr. Carley's ethics assessment of the studies. He noted that obtaining ICFs, IRB documentation, or protocol information for review of previously published work would be useful, if the article was published recently enough to make this possible.

Dr. Menikoff continued that these studies were unusual in the context of determining LOAEL because their primary objective was to measure a therapeutic effect. As Dr. Fitzpatrick noted, the risk-benefit ratio for this population of patients with serious conditions may be different than that for the general population. MS and SCI are serious conditions with few treatment options. There is good evidence based on pharmacological data that 4-AP could be beneficial. The studies also indicate that the side effects associated with treatment are likely to be minimal and reversible. It is appropriate to conclude, therefore, that the risk-benefit ratio was appropriate. All three studies claimed appropriate informed consent, which the Board must assume in the absence of clear and convincing evidence that contradicts this. All studies also were reviewed by an IRB or its equivalent. Given the available information, it is difficult to conclude that these studies were fundamentally unethical or that there is clear evidence of deviation from prevailing ethical standards.

Dr. Brimijoin summarized that the Board concluded there was no clear and convincing evidence that the studies were unethical or failed to meet prevailing ethical standards.

Overview of AEATF and AHETF Research Programs

Mr. Jordan provided an overview of the AHETF and AEATF. Three protocols from the AHETF were presented at a previous HSRB meeting. At the meeting, the Board indicated that the materials presented were not sufficient for a substantive evaluation to determine the scientific reliability of the data that would be generated or to determine if the protocols met ethical standards. The Board raised a number of scientific and ethical questions for EPA to consider. This led to a January 2007 meeting of the FIFRA SAP at which information related to scientific issues raised by the HSRB were discussed. The information presented at the April 2007 HSRB meeting focused on the social value of the proposed research, i.e., had EPA demonstrated the

need to collect new data on agricultural handler exposure. The Board agreed with EPA's assessment of the need for new data to assess handler risk. Discussion at the April 2007 HSRB meeting also addressed broad issues applicable to all protocols that the HSRB will review in the future.

The goal of AHETF and AEATF discussions at this meeting was to ensure that the task forces and the HSRB are ready to present and review materials and protocols meaningfully, namely that the task forces will be able to provide all information necessary for a meaningful review of protocols by the HSRB.

Mr. Jordan described several broad issues related to the charge questions in this meeting's transmittal memorandum. The issues included the following:

1. An overview of task force materials, to ensure that terms are understood and used correctly;
2. Balancing of risks and benefits in this research to ensure that the benefits justify the risks to participants and to ensure that this question is properly framed;
3. The potential for underestimation bias, which reflects certain aspects of the methods used to collect pesticide residues on handlers, including passive dosimetry, hand rinse, and face wipe;
4. Biomonitoring as an alternative, or in addition to, passive dosimetry;
5. Quality assurance (QA) and control procedures developed by the task forces to ensure that results are scientifically reliable;
6. Task force proposals to use purposive diversity sampling as an alternative to stratified random sampling;
7. The number of monitoring units and how to cluster these units in terms of the precision to be achieved;
8. Repeated measurements that would enable characterization of the degree of within-worker variability;
9. Ethics issues including risk minimization and recruitment issues, especially of non-native English speakers.

EPA seeks advice on scientific issues that will ensure the data are scientifically reliable and whether the planned approaches will affect reliability of results and that the results will be of sufficient value to justify subject risk. The Board should consider the value of this data compared to existing data in the Pesticide Handler Exposure Database (PHED). EPA also asks whether the proposed research designs use its resources efficiently and provide a significant return-on-investment. EPA wishes to consider the value of increasing funding to collect additional data. The Board should consider whether EPA is cognizant of relevant risks for this work and if information is available and correct for making decisions concerning risks and benefits.

Overview of Handler Research

Mr. Carley described documents provided by the task forces and the planned designs of the databases. The task forces provided documents describing standard operating procedures (SOPs); AEATF has not completed its SOPs but has included a sample protocol including a description of the informed consent process.

Each task force has developed governing documents that provide a description of the programs at the highest level. Each task force has a number of different scenarios; for example, the AHETF has 37 different scenarios. A scenario is described as a specific pesticide handling situation defined by data gathered under common properties. The governing documents have statistical design and recruiting information at a general level. Design and recruiting processes will be made specific to each scenario. Each scenario could be viewed as a distinct research project; scenarios will have specific research plans, and will collect and analyze data.

Data to populate each scenario will be collected in clusters. A cluster is a set of related handler data from each scenario. Within each cluster will be monitoring units (MUs). A MU is not a subject but instead should be thought of as a string of data. The AHETF calls for five MUs in each of five clusters to populate a scenario. The AEATF plans to have six MUs in three clusters. This may not work for all scenarios and more appropriate designs can be developed if needed.

Mr. Carley described how a proposal for a specific field study would fit into the program, contribute to the database, and be presented to EPA and the HSRB. A field study is a convenient group of MUs with a related protocol and final report, both of which will be reviewed by EPA. MUs will fall within a single cluster, which can be defined generally as a location. Within a cluster, MUs can represent different types of handling, for example mixing/loading or application using different types of equipment. The data gathered within such a cluster may apply to different scenarios. The task force will write the final report after data have been entered into a cluster and then into a scenario. For the AEATF database, all MUs required to fill a cluster are part of different field studies. When the design of each scenario is fulfilled, scenario-level analysis can begin.

The HSRB review will have to consider each scenario design and its appropriateness. When a completed study is reviewed, the Board will consider whether the study fulfills the requirements of its protocol and also contribute to the scenario-specific design. The task forces will not perform scenario analysis without all necessary data, but may reconsider the scenario design when analyzing a completed field study.

Dr. Fitzpatrick questioned whether a MU would be assigned to one or multiple scenarios. Mr. Carley replied that he would need to discuss this with task force leaders. Dr. Fenske described a cluster as a space and temporal event, describing the location at which a field study would be performed and asked whether more than one field study would contribute to a cluster. Mr. Carley added that it was unclear how best to consider a field study involving, for example, 10 to 12 MUs that could contribute to multiple scenarios. Such a situation could be considered two clusters that occur in time or space or could be considered one cluster that feeds multiple

scenarios. Dr. Fenske remarked that data from a field study likely would contribute to multiple scenarios. He asked whether one field study would take place at one cluster, or if multiple field studies could occur at one cluster. Mr. Carley noted that either situation could arise. For example, if there are fewer usable MUs from a field study, data from another field study may be needed to fulfill the statistical design.

Dr. Fenske inquired whether it was correct to assume that the first protocol the Board reviews will have multiple scenarios because of differences between mixer/loader and applicator exposures. Dr. Chambers questioned if scenario design would be related to the protocols. Mr. Carley explained that the Board will receive information on scenario design along with the protocol. The challenge for the review schedule is that, in addition to developing protocols, a presentation of scenario design also must be developed. Dr. Chambers asked whether the protocol for the field studies may have multiple scenarios, and, if this were the case, would different sampling strategies be described in the same field study. Mr. Carley responded that some field studies would have multiple scenarios and different sampling strategies. For example, if the study includes mixer/loader and applicator exposure, there will be two scenario design documents and one protocol. These data may feed into a single cluster. Dr. Brimijoin thanked Mr. Carley for his explanation of the task force designs and noted that analysis of specific protocols will probably help clarify any remaining questions.

Risks and Benefits of Handler Research

Mr. Carley presented his review of the risks and benefits associated with the exposure monitoring programs. He stated that he was not asking the Board to reach a conclusive judgment regarding risk and benefits at this time. He continued by stating that at the level of the Governing Documents, conclusive weighing of risks and benefits is impossible, because knowledge of the risks associated with a specific field study and of the benefits specific to a specific scenario are required. Risks to subjects can be characterized in general terms, and potential ways of minimizing risks and potential benefits of the research can be identified.

Categories of subject risk described, in descending order of risk, by the AHETF include heat-related illness, exposure to surrogate chemicals, risk associated with scripted activity, psychological risk, risk from exposure to detergent rinses, and the background risks of agricultural work. Risk categories described by the AEATF include chemical risks related to use of a surrogate antimicrobial chemical and exposure to alcohol/water face and hand rinse solutions. Physical risks may arise from heat stress or exaggeration of normal activities. Psychological risks also will be considered.

Heat-related risk arises from the increased requirement for additional layers of clothing (passive dosimetry) and also possibly from scripted activities. This risk rises with the heat index. Heat-related risks can be minimized by training, the presence of onsite medical staff, provision of liquids and shade, close observation, monitoring the heat index, and developing clear stopping rules. In addition to stopping rules, “non-starting rules” that will prohibit commencement of study based on the heat index also will be developed. With these precautions, residual risk is likely to be acceptably low. Concerning risk from surrogate chemical exposure, the use of registered pesticides as directed are unlikely to cause unreasonable adverse effects. Ensuring

that workers follow all label and Worker Protection Standard (WPS) requirements for protective clothing and personal protective equipment (PPE) will minimize risk. A residual risk is that of irritation in the event of a spill.

AHETF "scripting" may increase the length of the workday, or the amounts of active ingredient handled, or call for use of less familiar equipment. This risk can be minimized by the same methods used for risks of heat stress and active ingredient exposure, with the addition of the opportunity to practice with any less familiar equipment. AEATF "exaggerating activity" may lead to fatigue or heat stress, which can be minimized by careful study-specific design and by close observation of subjects. If these precautions are implemented, residual risks are likely to be low.

Two types of psychological risks have been identified, namely risks associated with taking a pregnancy test and risk of embarrassment while changing clothes to put on passive dosimetry garments. Both these risks can be minimized by actions to ensure privacy. If these procedures are implemented, residual risks are likely to be low.

Some degree of risk is associated with use of hand rinse or face wash solutions. AHETF expects to use 0.01 percent detergent in water and AEATF proposes using 50 percent isopropyl alcohol (IPA) in water. The risk associated with these solutions is primarily irritation. This can be minimized by supervision by a technician when rinsing near the eyes, close observation for signs of irritation, and a clear stopping rule. Any residual risks are likely to be low.

The background risk of agricultural work is primarily of injury arising from possible increased use of less familiar equipment, and also dizziness or confusion attributable to early heat-related illness and exposure to other chemicals. The choice to apply chemicals, in addition to those under investigation in the protocol, is not under the control of the investigators, but instead is a decision made by the owner of the field. This cannot be comprehensively addressed in protocols but could be minimized through good agricultural practices. The task force will ensure that compounds required by the owner will not interfere with analysis of results. It also should be noted that the additional chemicals might not be pesticides but instead could be substances, such as fertilizers.

There is no direct benefit of this research for the subjects, but there are possible indirect benefits if the research leads to better safety standards. The potential societal benefits of knowledge likely to be gained should be assessed primarily at the scenario level, taking into account existing data, the appropriateness of normalization factors, and scenario-specific sampling designs. The benefits of improved estimates of handler exposure and potentially improved protection of workers can be realized only when the scenario-level design is fulfilled. Potential benefits to AHETF members include conduct of monitoring programs that keep them in regulatory compliance. For growers and landowners, the provision of free product may more than offset the disadvantages and inconveniences of cooperating in the research.

When weighing risks and benefits, the task force monitoring programs will include only studies designed to fill established needs for new exposure data. Scenario-specific designs will include full discussions of anticipated societal benefits. Study proposals will include discussions

of the balance between study-specific minimized residual risks and anticipated benefits at the study level (if any) and at the scenario level. EPA believes the benefits of this research are likely to outweigh the minimized risks to subjects. The Board is asked to consider whether the Governing Documents, in addition to the described information on risks and risk minimization, provide an adequate basis for assessing whether the risks of a particular study are justified by the expected benefits of the proposed research, and if not, to describe additional information that should be provided to an IRB, EPA, and/or the HSRB.

Dr. Chambers questioned whether additional PPE would be recommended if it was found that exposure was higher than expected and whether this could be assessed before the scenario-level analysis was performed. Mr. Carley explained that each field study will generate a report that will be reviewed by the HSRB. The statistics-driven analysis of the association of active ingredient handled with exposure will not be performed until the scenario-level data requirements are fulfilled. There are also statutory regulations that require prompt submission of any evidence of unexpected adverse effect; EPA expects that any unexpectedly high exposure will be brought quickly to its attention.

Public Comment

Dr. Richard Collier on behalf of AHETF

Dr. Richard Collier (AHETF) clarified that for the AHETF studies, a single MU will be assigned to only one scenario. One MU represents a person who is being monitored and all aspects of his work practices and the environmental conditions associated with a given activity. In most cases, a field study will contribute data to only a single cluster; however, this distinction may not be important. Given a study with mixer/loader activities, as well as an MU performing application activities, this would represent parts of two clusters but would be assigned to one scenario. A study can be thought of as activities performed in the field and the protocol that defines these activities. Dr. Collier added that the plan is for the HSRB to review documents that define one scenario, one clusters, and one study protocol within that scenario at the October 2007 HSRB meeting.

Dr. Fenske questioned whether a given field study was likely to include people performing different activities (such as mixing, loading, and application) and if data from these activities would apply to different scenarios but would still be part of the same cluster. Dr. Collier explained that these would be considered different clusters because they describe different activities. From a statistical perspective, to analyze cluster-level effects, this single study would involve more than 1 cluster. Dr. Fenske clarified that he believed this study would have two types of MUs whose information is entered into different parts of the database. Dr. Lebowitz inquired whether data applicable to two scenarios could be gathered from the same site at the same time and whether this would constitute conduct of two studies or protocols or just one. He asked whether a protocol would be developed for each type of work. Dr. Collier responded that such a study would involve two sets and types of MUs. The AHETF views this as one study, because a study is an activity performed in a field in a particular place at a particular time. Dr. Fenske commented that this appeared to be analogous to doing indoor air pollution studies in a single home in which data would be collected on both adults and children.

The sampling may be performed differently for each group and the data may be sent to different bins for analysis, but this would be considered one field study.

Board Discussion

Dr. Fenske opened discussion of the charge questions. He noted that EPA has been responsive in supplying governing documents for task force work, but despite this there continues to be confusion around terminology such as "MU." Concerning risks and benefits of handler research, Dr. Fenske agreed with Mr. Carley's assessment and the description in the reports by the two task forces. He commended Mr. Carley and the task forces for identifying potential hazards or risks and developing ways to minimize these risks. Dr. Fenske stated that the range of risks described was comprehensive and each description of ways to minimize risk was thoughtfully performed. He stated that this analysis builds confidence that the studies will be carefully conducted with attention to potential risks.

Concerning benefits, Dr. Fenske agreed that only indirect benefits would accrue to participants in the form of better data leading to better protection policies. He also agreed with Mr. Carley's consideration of the benefits to growers and landowners in the form of free product compared to the inconvenience of participating. Dr. Fenske added that another potential benefit for growers is better data that could lead to less over-regulation of chemicals that may not need to be strongly regulated. The data gathered in these studies could help ensure that products are not inappropriately removed from the market. Dr. Fenske noted that under FIFRA, benefits of this work can apply to users, but not to the manufacturers. Mr. Carley agreed that analysis of risk and benefit related to registration decisions was appropriate. He noted that his analysis examined only the benefits attributable to conducting the studies, which will help keep task force members in regulatory compliance. Dr. Fenske continued that he agreed that the primary societal benefit was that of better science to improve risk assessment and public policy. He concurred that for these studies, benefits significantly outweighed risk.

Mr. Paul Hamey (Consultant to the HSRB) provided the perspective of a grower in the United Kingdom. He agreed with EPA's analysis of risks and benefits. He added that although the governing documents indicate no direct benefit to the participants, one direct benefit could be feedback on individual performance in the context of a study that could improve handlers' practices and decrease exposure. He asked for comments on appropriate actions if a study director noticed an individual operator using unsafe practices. For example, during a series of studies by a United Kingdom task force, it was noticed that handlers commonly used compressed air to clear build-up from equipment; this generates aerosols and increases exposure. In response to this, the task force developed and provided a poster to increase awareness of this issue and promote safer means of cleaning equipment.

He stated that the governing documents provided a good discussion of risk and added two additional risks: mechanical injury arising as a result of collapse of a hydraulic system and electrical injury through equipment contact with liquids. If a study participant is asked to use unfamiliar equipment because of scripted activity, the risks of either of these events increases. The governing documents discuss requiring familiarity with equipment and provide for practice with unfamiliar equipment, but do not consider existing standards for using new equipment; in the United Kingdom, training and a formal test are required. Mr. Hamey commented on the

heat-related illness mitigation procedure of encouraging participants to drink more water and noted that this may increase exposure by the oral route. Drinking while working with hazardous substances contradicts governing document statements regarding safe practices when drinking at work.

Dr. Chambers stated that her review was similar to Dr. Fenske's, and acknowledged the strengths of the governing document. She noted that a conceptual problem was estimating potential risks of exposure to chemicals which would require use of a MOE and asked how the MOE could be calculated. Mr. Jordan clarified that all chemicals used in task force studies have been subject to EPA risk assessment using existing exposure data in the PHED. The task force uses the PHED value as an assumption about the degrees of exposure occurring in a scenario and applies that to the amount of active ingredient handled. Dr. Chambers thanked Mr. Jordan for the clarification and asked that a review of the studies' structure, with respect to MUs, clusters, and scenarios, be presented at the October 2007 HSRB meeting.

Dr. Lebowitz commended EPA on the thorough documentation of its analysis. He noted that risks related to financial concerns and job security were not discussed; he was informed that this would be discussed during the meeting. Dr. Lebowitz questioned whether agricultural handlers would learn or be reminded of best practices during the course of the studies, noting that observation by study personnel may discover that some handlers are using inappropriate methods for handling pesticides. He also asked how exposure to families upon workers' return to their homes would be assessed and whether risk to bystanders of accidental exposure during pesticide application would be considered.

Dr. Philpott inquired whether either task force had considered whether there would be unacceptable levels of risk associated with the potential for heat-related illnesses. He noted that the heat index would be used to create stopping rules, but the heat index makes assumptions of physical attributes such as height, weight, gender, ethnicity, movement, and clothing. Those participating in passive dosimetry studies may be wearing extra layers of clothing and some participants may have higher activity levels in direct sun than is assumed by the heat index. These considerations should be used to develop additional safety factors. He noted that the report categorizes extreme danger as a heat index of 130 degrees Fahrenheit (^{o}F) or higher, but at a heat index of 105^{o}F, the risk of sunstroke, heat cramps, and heat exhaustion increases. A lower heat index may need to be considered to trigger the stopping rule.

Dr. Popendorf (Consultant to the HSRB) questioned why compensation was not considered as a benefit. Dr. Brimijoin noted that the HSRB had specifically been asked not to consider this. Dr. Popendorf continued that another benefit to participants could be providing an option for participants to learn about their exposure levels, which could result in decreases in unsafe practices. He added that clarification of growers' benefits also is needed.

Dr. Brimijoin summarized that the Board was impressed with the progress and efforts of EPA in preparing these documents. Concerning the discussion of potential additional benefits, he commended EPA for raising the issue of benefit to landowners being mitigated by the inconvenience of participation. There is a danger of landowner benefit resulting in coercion of workers to participate. Dr. Brimijoin acknowledged Mr. Hamey's contributions regarding

potential educational opportunities through identification of unsafe practices at the individual and site levels. Plans should be developed to capture this potential benefit. Regarding scripted activities, it will be advantageous for workers to use familiar equipment as much as possible. Other issues raised included the wisdom of urging increased fluid consumption to mitigate heat-related risks because this could increase risk of pesticide ingestion. Dr. Chambers raised questions concerning error calculations that were answered by EPA. Dr. Lebowitz raised questions concerning minimizing exposure to families and assessing risk to bystanders. Dr. Philpott suggested that EPA reconsider heat index levels used to set stopping rules. Dr. Popendorf mentioned knowledge of individual exposure levels as a potential benefit for participants.

Addressing Potential Sources of Underestimation Bias

Mr. Jeffrey Evans (OPP, EPA) presented EPA's analysis of potential sources of underestimation bias. The task forces will rely on whole body dosimeters (WBD), hand rinse/washing, and face/neck wipes to determine exposure. EPA has analyzed whether concern for breakthrough and/or collection/removal efficiencies of passive dosimetry techniques warrants adjustments to field measurements. EPA sought the advice of the FIFRA SAP in January 2007 on a number of topics related to the potential for underestimation bias of passive dosimetry, including comparison of passive dosimetry and biological monitoring studies, analysis of hand measurements in the current PHED, and a review of available literature related to hand rinse techniques.

Comparison of whole body passive dosimetry and biological monitoring suggested a lack of systematic bias between methods; both methods yielded similar results, suggesting that both give reasonable estimates of exposure. Thus, passive dosimetry is not likely to substantially underestimate exposure that may be caused by dermal absorption during sampling or breakthrough of dermal dosimeters. The SAP concluded that bias may exist, but bias between dermal exposure and biological monitoring could not be detected in part because of the statistical uncertainty inherent in exposure data. The SAP also noted that passive dosimetry can generate data that can be used to develop predictive estimates of exposure for a number of different scenarios and activities. The SAP suggested that biological monitoring could be a useful check on passive dosimetry or to measure WBD breakthrough, but declined to require biological monitoring in a protocol. EPA agreed with the overall SAP conclusions and described some disadvantages to biological monitoring including additional cost, logistical considerations (number of days required for metabolites to clear), and a lack of acceptable biomonitoring methods for all surrogates.

The SAP also assessed potential underestimation bias resulting from determining exposure by hand washing. The literature indicates that hand wash/rinse performance can be influenced by the chemical properties of the pesticide, such as solubility, octanol/water partition coefficient, or formulation type; residence time on the skin before hand rinsing is performed; type of solvent used to rinse the hands (e.g., alcohol, soap and water); concentration of the chemical on the skin (microgram/cm^2); duration of the exposure monitoring period; and nature of the residue (whether exposed to pesticide concentrates, dilute sprays, or field residues). The literature also indicates that hand rinse removal efficiency values from studies involving human

subjects ranged from approximately 70 to 90 percent for many of the surrogate compounds selected by the AHETF (with the exception of chlorpyrifos, which has an efficiency of approximately 20 to 40 percent). An AEATF hand rinse efficiency study indicates up to 90 percent efficiency for didecyl dimethyl ammonium.

Face/neck wipes were not specifically discussed at the SAP meeting nor are they presented in the 1987 Subdivision U, Agency guidelines. Face/neck wipes have been widely used since the late 1980s or early 1990s and are an option in Organization for Economic Co-Operation and Development (OECD) guidance; series on Testing and Assessment No. 9. Investigators generally use the same solvents or surfactants for both hand rinses and face/neck wipes. Exposure to the head/face and neck is expected to be very low for the majority of exposure scenarios planned by the AHETF. An exception to this can be seen in a series of existing AHETF open cab airblast studies, in which both face/neck wipe and patch data (outside and inside chemical resistant headgear) were collected to determine potential exposure for these areas. Face/neck wipes will be treated the same as hand washes when making corrections.

The SAP was equivocal about the need to correct the results from hand washing for its efficiency at recovering pesticides from skin. The SAP would accept a rinse validation study if it can decrease the uncertainty at a reasonable cost and be done within approved human subjects study guidelines. Some panel members recommended using modeling to adjust hand exposure and offered as an example an algorithm based on some of the literature cited by the Agency in the SAP documentation. Others noted weaknesses in both modeling and validation study approaches and raised concerns about potential confounding by field conditions (i.e., effects of repetitive rinsing that may change the skin's absorption rate).

EPA has concluded that for the proposed AHETF studies, the contribution of hand exposure is expected to be minimal because all subjects will be wearing chemical resistant gloves (CRG) during all operations. AEATF intends to collect data based on individuals not wearing gloves (consumer products). For most scenarios, significant exposure to head, face, and neck is expected to be low. A series of options for considering this has been proposed to AHETF. Biological monitoring can be included as a check for potential breakthrough or other losses when using surrogates that have well-established methods. The use of cotton gloves beneath the CRG and the use of hat patches when measuring head, face, and neck exposures for scenarios having the potential for overhead exposures (e.g., open-cab airblast) could be considered. Conditions should be established for correcting hand rinses and face/neck wipes. EPA has proposed a set of conditions for consideration by both task forces, namely, if measured exposures from hands, face, and neck contribute less than 20 percent of total exposure, no action is required, but if measured exposure contribution represents between 20 and 60 percent of total exposure, an automatic 50 percent adjustment can be made or a validation study can be submitted. If measured exposure contribution is greater than 60 percent, a validation study is required. Because validation studies involve intentional dosing of human subjects, review of these studies by the HSRB will be required.

AHETF has concluded that no correction is needed for any potential method bias because of reasonable congruence in exposure estimates between studies based on biological monitoring and those using passive dosimetry. AEATF has concluded that no correction is needed in studies

where individuals will not be wearing gloves and the hand correction factor is reasonable. EPA has concluded that substantial underestimation by WBD is unlikely and the Agency believes that the hand wash, face/neck wipe options are the most appropriate for correction of potential underestimations using these techniques.

The Board was asked to consider whether EPA had identified the relevant scientific and practical considerations affecting the choice to include biomonitoring and appropriately characterized the limitations on the scientific usefulness of the resulting data if no biomonitoring is conducted. If not, the HSRB should describe other considerations that should bear on a decision to conduct biomonitoring in addition to WBD. The HSRB also is asked to consider whether EPA had appropriately characterized the limitations of the scientific usefulness of a handler database that does not include data characterizing the efficiency of residue removal procedures.

Dr. Chambers inquired how exposures of 20 percent or less would be assessed if there is insufficient exposure data to determine this. Mr. Evans replied that the analysis will have to rely on old data, and that decisions concerning this matter will be made as the data accumulates. Dr. Lehman-Mckeeman questioned if the biomonitoring samples would be taken from urine. Mr. Evans responded that this was correct. She inquired whether the availability of well-established methods would be the only criterion for determining if biomonitoring could be used to check for breakthrough and asked whether the feasibility of collecting samples based on the half-life or absorption of a compound should also be considered. Mr. Evans explained that these parameters also would be considered; if analysis of a certain compound required sequestering participants for several days, biomonitoring of that compound would probably not be performed.

Dr. Popendorf noted that if skin recovery data was required, human exposure protocols would be needed; however, to simply determine recovery, *in vitro* substitutes for human skin are available, and use of cadaver skin also could be considered.

Quality Control and Quality Assurance in AHETF and AEATF Occupational Handler Monitoring

Mr. Jeff Dawson (OPP, EPA) presented Agency activities concerning quality control (QC) and quality assurance (QA) procedures for the AHETF and AEATF protocols. He opened by defining QA as a program for the systematic monitoring and evaluation of the various aspects of a project, service, or facility to ensure that standards of quality are being met and QC as operational techniques and the activities used to fulfill and verify requirements of quality.

EPA uses GLPs under FIFRA and the Toxic Substances Control Act; GLPs were implemented by EPA in 1989. Key elements for occupational monitoring include documentation throughout each phase, specific requirements and formats for protocols, establishment of SOPs for all phases, audit of each study phase and general issues (e.g., QC maintenance records), establishment of personnel training records, establishment of lines of communication and responsibility, and definition of the fines and criminal penalties possible for non-compliance. Field investigators and laboratories are required to work under GLPs. A number of SOPs

pertaining to QA and QC were developed as a collaborative effort involving both task forces, EPA, California EPA Department of Pesticide Regulation (CDPR), and the Canadian Pest Management Regulatory Agency (PMRA). The SOPs are essentially identical in scope and verbiage in many cases; thus, AHETF SOPs were presented as an example. The SOPs address all elements of occupational study conduct, including administration, protocol development, the field phase, analysis, and reporting. The AHETF governing document has 11 SOP chapters.

SOP 1 pertains to administration and covers organizational structure, responsibilities, inspections, and external communication. The study director has overall responsibility and ensures protocol compliance, addresses addenda and deviations, and takes corrective action in response to unforeseen circumstances. The principal investigator (PI) provides a direct line of communication between a facility and the AHETF study director. Ethics training also falls under this SOP. The QA unit (QAU) is an independent entity that reports directly to the task force manager and study director.

SOP 2 covers initiation, development, and content of protocols that dictate study conduct. Protocols should link GLP requirements and SOPs. This SOP also establishes a protocol approval process, and each protocol will specifically reference the appropriate SOPs. Amendment and deviation processes are part of this SOP.

SOP 3 describes development of SOPs, including format; preparation and approval; review, revision, and retirement; distribution; and consideration of contractor SOPs.

SOP 4 describes study report content, format, and submission requirements.

SOP 5 describes the scope and responsibilities of the QAU. The QAU, as described in SOP 1, is a separate third party that reports to AHETF management. The QAU oversees GLP-required elements, such as communication with management and recordkeeping. Facility inspections and protocol, data, and report audits are the responsibility of the QAU.

SOP 6 establishes archive processes for records and specimen/sample storage. This SOP describes requirements for raw data storage, QAU audit storage, formulated product or standard materials, and confidential worker information.

SOP 7 oversees test, reference, and control substances, including shipping, receiving, storage, and tracking of test materials. Also included in this SOP are labeling and tracking requirements (such as chain of custody forms), container retention, and the AHETF test substance definition (“All registered pesticides that may be used on an AHETF study for the sole purpose of providing detectable residues in the determination of a pesticide exposure profile”).

SOP 8 pertains to matrix samples, including sample media, sample collection, storage and labeling, and QC procedures. For each monitoring method, pre-field preparation and in-field sample procedures will be addressed, as well as QC elements (for example, positive WBD controls to evaluate losses due to conditions during the sample collection period). This SOP also will review workers’ personal apparel for compliance with WPS and develop systematic sample tracking codes.

SOP 9 covers analytical detection, data corrections, and paper and electronic elements. Concerning analytical elements, this SOP requires corrections to be proposed based on field recovery estimates. Analytical elements include the limit of quantitation (LOQ), which is the lowest level fortified for a matrix in a study; limit of detection (LOD) is 0.3X LOQ. If mean field recovery is less than the LOQ, one-half of the LOQ will be used for corrections. This SOP also defines methods for recording data, including GLP error codes, and provides details for authenticating copies and portable document format preparation.

SOP 10 defines field study operations, including processes for equipment calibration and field/worker data collection. This SOP describes methods for air samples (e.g., primary standards), application equipment (e.g., flow meters), worker observation criteria (e.g., motions, out of scope activities such as not wearing PPE), environmental conditions (e.g., wind speed, direction, temperature, humidity, etc.), and sample shipment.

SOP 11 covers human subject management, including ethics training, recruitment, language requirements, and informed consent. Worker recruitment, language issues, pregnancy status, hazard information, unanticipated adverse events, and heat stress management (National Oceanic and Atmospheric Administration and National Weather Service criteria) also are covered by this SOP. SOP 11 helps ensure ethical compliance and identifies Agencies and rules pertaining to this issue.

Development of these SOPs represents a collaborative effort involving the task forces and multiple federal and other agencies. The results of recent SAP and HSRB reviews have been incorporated into SOP development. The scope of the SOPs includes the task forces and associated contractors, and requirements of the SOPs are dictated in part by GLP requirements.

In collaboration with officials in the Canadian PRMA and the CDPR, EPA has worked with the task forces as they developed a set of SOPs to ensure the data resulting from their proposed research is of high quality. The task force SOPs reflect current, state-of-the-art methods for QA and QC in the collection, storage, and analysis of analytical samples. Therefore EPA believes that the resulting data will be of very high quality. The Board is asked to evaluate whether the SOPs are adequate to ensure high quality data results from the proposed research, and, if not, to describe other QA or QC procedures that need to be addressed.

Public Comment

Dr. John Ross of Infoscientific, Inc. on behalf of CropLife America

Passive dosimetry methods, such as air monitoring and dermal monitoring using clothing dosimeters (inner and/or outer), hand washes, or face/neck wipes, have been established with national and international input from experts. Biomonitoring is not viable for a generic database and cannot be performed for many compounds because of a lack of pharmacodynamic/pharmacokinetic data. A recent study (Ross et al., 2007) demonstrates that concurrent passive dosimetry versus biomonitoring shows that passive dosimetry neither under- nor over-predicts exposure. A graph comparing concurrent passive dosimetry with

biomonitoring using results from a number of studies showed neither an over- nor underestimation bias.

Hands can represent a significant proportion of total dermal exposure. A combination of soap, water, and mechanical agitation is the primary method of hygiene for removal of pesticide residues on hands and very effectively removes most compounds. There is a great deal of GLP available to regulators to determine the removal efficiency of pesticides from skin, including more than 80 dermal absorption studies in rats with soap and water removal and more than 10 human/monkey dermal absorption studies with soap and water. Most of this data was generated using radio labeled pesticides to ensure accountability. Data from more than 20 human/monkey dermal absorption studies of different pesticides indicate, on average, less than 10 percent absorption following an 8-hour exposure. Data from rat studies show that what is adsorbed is frequently absorbed, although a few compounds have bound skin residues (adsorbed) that are 2 to 3 times greater than absorbed. Quality hand removal efficiency studies show that more than 90 percent of a compound on the hands can be removed.

Hand wash methods can overestimate exposure. Most measured residues would slough or wash off the hand during the work period, so only a fraction of the amount applied is dermally absorbed. In addition, pesticide frequently is adsorbed to dirt on the hands, reducing bioavailability. Pesticide washed off in the first half of the day has no opportunity for absorption, but may be counted as if it did in some protocols. Any task that requires gloves also reduces hand exposure 10-fold or more compared to an ungloved hand wash.

If hand wash removal efficacy studies are planned, investigators must be aware that applying a dose of a substance to clean hands may not simulate agricultural work conditions. Under these conditions, hand exposure is intermittent and does not occur as a bolus, which is typical of a hand wash removal study. Removal efficiency also is related to concentration, and a worker may be exposed to both dilute and concentrated pesticides. Use of radio labeled pesticides would insure accountability of total dose, but the risks of this approach may outweigh the benefits.

Dr. Ross concluded that the weight of evidence indicates that dermal removal efficiency is adequate. There are questions about the applicability of short-term removal efficiency (0.5 hour) to typical worker removal time (2 to 8 hours). Without reason to believe that recovery may be compromised (e.g., high reactivity, polarity or lipophilicity), a removal efficiency study is unjustified. If hands represent 50 percent exposure and 10 percent is lost due to adsorption/absorption, underestimation is 5 percent and is negligible.

Dr. Lehman-Mckeeman requested clarification of the graph presented by Dr. Ross. Dr. Ross explained that each point on the graph represented an individual. The graph has data from eight or nine different chemicals from 14 different studies and more than 24 different exposure scenarios. Some of the studies are worker re-entry studies, others assessed exposures during application. A number of the compounds are the same as those that will be used in AHETF studies.

Dr. Philpott addressed Dr. Ross' argument that without reason to believe recovery was compromised, an efficiency study is unjustified. He noted that Mr. Evans had mentioned that one of the compounds in question (chlorpyrifos) had an unpredicted low rate of recovery and asked whether Dr. Ross would have predicted this. Dr. Ross answered that approximately 20 percent of the points in the graph represent chlorpyrifos chemicals. The assertion that the recovery rate was only 10 to 20 percent is questionable because the experiments did not use radio labeled material. Dr. Lebowitz inquired whether oral exposure (i.e., ingestion of pesticide-contaminated foods) would affect bias and how this could be determined if biomonitoring is not performed. Dr. Ross responded that the data on the graph were largely generated using worker exposures. In most cases, any contribution of exposure from diet was subtracted using background levels described by the CDC National Biomonitoring Program. Handlers' dermal exposure is at least an order of magnitude higher. Dr. Fenske noted that the data on chlorpyrifos came from studies he had performed and that in these experiments, all mass except for that stuck to the skin was collected.

Dr. Ray McAllister of CropLife America

Dr. Ray McAllister presented comments from a regulatory perspective concerning the issue of adjusting hand and face exposure by a removal efficiency coefficient. He reiterated that data show that the guideline passive dosimetry methodology in question does not have a systematic bias nor does it underestimate exposure. Because of this, he questioned the need for a correction factor to apply to data generated by guideline studies. EPA has proposed either arbitrary adjustment factors that vastly increase hand/face exposure estimates or requiring removal efficiency studies whenever the hand/face exposure estimate is 20 percent or greater of the total exposure; this is likely to result in a required efficiency study. He suggested that the HSRB should ask EPA to define such studies (i.e., what loading factor should be applied to a human subject's hand, how long should the substance remain on the skin before removal, and whether pipette administration of a pesticide to hands over a 5-second period is similar to the dynamics of deposition and removal over a full day of agricultural work activities). Because of these questions, data may be uninterpretable, leading to the conclusion that intentional human exposure in such studies would be unethical on grounds of inadequate scientific validity.

It is possible and preferable to determine the qualitative potential for high hand or face exposure from the use pattern. For example, if a pesticide concentrate is handled with unprotected hands, hand exposure would be expected to be a high percentage of the total exposure. If this is demonstrated in a study, the expected result (i.e., proportionally high hand exposure) should not be penalized by applying an adjustment factor. If the data do not demonstrate what was expected, further investigation is warranted. This is the opposite of what EPA has proposed.

Exposure assessment for determination of risk incorporates various uncertainty factors unique to each assessment. These factors involve pesticide use information, robustness of the toxicology database, and specific laws under which the data are being evaluated. Dr. McAllister stated that EPA's recommendation of an across-the-board adjustment factor without consideration of these unique factors will introduce overestimation to the exposure assessment and will diminish the accuracy of the assessment. He agreed that there may be unique

circumstances that call for adjustments for hand rinse efficiency studies, but each regulatory agency should determine the need on a case-by-case basis, not by an across-the-board decision by any one regulatory agency or the HSRB.

Dr. McAllister noted that AHETF and AEATF followed EPA guidelines that are consistent with international OECD guidelines and were developed in an open process involving multiple public meetings. Any considerations of changes to the guidelines must involve public debate on the impact on the methodology as a whole and on the overall risk assessment process. He contended that the HSRB meetings do not provide such a forum. He concluded by stating that requiring a hand/face correction factor will not ensure extra protection for handlers but may generate an overestimation of exposure that could lead to higher-tier human exposure studies that would not have been planned if the initial assessment had been more accurate. The current methodology provides adequate accuracy without adjustments.

Day 3

Follow-up from Previous Day's Discussion

Mr. Jordan thanked the Board for the advice given in previous sessions and stated that EPA had no further questions at this time.

AEATF and AHETF Research Programs (continued)

Board Discussion

Addressing Potential Sources of Underestimation Bias

Dr. Fenske presented information related to potential sources of underestimation bias for the AEATF and AHETF research programs. He noted that biomonitoring is a potential means for evaluating the accuracy of passive dosimetry, but disagreed that Ross et al (2007), as presented during the previous day's session, made a solid case for validation of passive dosimetry using biomonitoring.

Hand wash and skin wipe techniques underestimate true dermal exposures; the question is by how much. The nature of the chemical in question and the removal method will affect the degree of underestimation. Interception (capture of the analyte before it reaches the skin) can overestimate exposure, removal (after skin contact) underestimates exposure, and visual inspection (using dyes or fluorescent compounds) is typically most useful for qualitative evaluation and worker education.

The term "passive dosimetry" is not intuitive because it measures exposure, not dose; correction factors are needed to determine dose. Passive dosimetry also can include a mixture of techniques (i.e., interception and removal), which makes dosimetry protocols complex. Although the Ross et al (2007) article claims that passive dosimetry methods used in the studies analyzed in this article have not been validated, the AHETF Human Research Monitoring Program states that there are validated passive exposure monitoring dosimetry techniques that

will be used in the AHETF field study program and that "basic passive dosimetry methodology has long been accepted as a standard, reproducible procedure that provides accurate and reliable data and does not underestimate exposure." Dr. Fenske noted that this is an overstatement because some passive dosimetry techniques are standard consensus techniques, but have not been validated. OECD guidelines state that "it is not possible to evaluate the accuracy of any procedure. The best that can be achieved for a hand wash or hand rinse method is a laboratory validation of the efficiency of recovery of material from the hands of human volunteers."

Dr. Fenske presented a graph illustrating the correlation between passive dosimetry measurements of chlorpyrifos exposure compared to biomonitoring results. The graph showed that passive dosimetry underestimated the biomonitoring results in a systematic manner. A similar analysis of atrazine showed a systematic over-prediction of the biomonitoring-based dose. To accurately estimate dose, input factors (such as dermal absorption and excretion fraction, which are specific for different chemicals) are needed in addition to dosimetry; these factors are not standardized or vetted. Additionally, it can be difficult to compare passive dosimetry results because of differences in techniques used to determine the amount of a substance on the skin. Biomonitoring also presents difficulties; for example, 88 percent of a dose of atrazine does not appear as an excreted metabolite.

Because EPA has proposed hand wash efficiency studies, standard procedures for these studies should be developed. Dr. Fenske presented an example of such a procedure. He described the mass balance calculation (mass removed by hand wash divided by mass transferred to the hand equals efficiency) to determine the amount of exposure. He noted that for chlorpyrifos, the residence time of the substance affects the removal efficiency, which can be a problem in the field given that handlers do not frequently or consistently wash their hands; higher amounts of chlorpyrifos would be absorbed in such a situation. A comparison of hand wash and hand wipe methods to determine exposure to the apple thinner azinphosmethyl showed that the calculated exposure rates differed based on the methods used. Use of gloves resulted in an overestimation by approximately 2.4 fold, hand wash captured 68 percent of the true exposure, and hand wipe captured 10 percent of the true exposure.

Dr. Fenske noted that most protocols assume "best practices" by workers, but this is unlikely to be the case, which inevitably will lead to bias. Constraints on best practices that will affect exposure include label compliance constraints and the possible occurrence of behaviors prohibited by the label; protective clothing constraints, such as the assumption that clothing is in good condition and is in proper use at all times; and equipment constraints, including the assumptions that the equipment is in good condition, properly calibrated, and is used to properly reduce the probability of accidents or need for repair.

Other concerns include the effect of observation on real-life use. Handlers will be aware that their performance is under observation, which could change the way they work; however, behavior tends to normalize with multiple observations. Motivational bias may also occur as handlers attempt to meet the expectations of the study director. Workers with good health and safety practices also are more likely to volunteer and workers with poor practices may avoid participation. The study duration may impact behavior; if the study lengthens the workday, fatigue may result in less attention to safety during equipment cleanup and repair, and this

exposure may not be captured by the study. The goal of the task forces is to create a distribution of exposures reflective of true exposure; however, because of the above-mentioned constraints, the high end of exposure may be truncated because of extra precautions.

Dr. Popendorf thanked Dr. Fenske for his presentation, and agreed with his conclusions. He reiterated the challenges of generating recovery data, but noted that these may not be as large as anticipated because useful recovery data could be obtained by using substitutes for human skin. Although human skin is not a simple membrane, washing only involves the top layer, so true human skin is not needed. Concerning the problem of low recovery of a substance during washes, wipes are less efficient than washing and more variable. Dr. Popendorf recommended that adjustment for wipe and wash recovery be added to the protocols.

Dr. Chambers commented that, given the uncertainties of passive dosimetry, performing biomonitoring appears logical; however, the SAP concluded that biomonitoring also is uncertain and that good pharmacokinetic/pharmacodynamic data is available for only a few compounds. Biomonitoring also requires a longer monitoring period and that workers not be exposed to a compound for a certain length of time prior to test days. She asked about the recommendation that workers wear cotton gloves beneath the CRGs and whether this would limit mobility and increase accidents.

Dr. Fitzpatrick requested the percentage of exposure that occurs on the hands and face compared to the body. Dr. Fenske explained that it is difficult to generalize and depends on the application method. Using an airblast open cab application process would result in a relatively high level of exposure and a relatively large amount of deposition on the face. The kind and effectiveness of protective clothing also will affect exposure. For example, workers wear gloves, but often take them off; answering cell phones has become a particular problem in this regard. This results in contamination of the hand, and after re-gloving, an occlusive atmosphere develops that may enhance uptake/absorption of substances on the hands. Dr. Fenske added that EPA's request for HSRB input on the need for additional data should be discussed at a future meeting.

Dr. Brimijoin noted that the high degree of uncertainty inherent in passive dosimetry is frustrating. He said that the question to address is whether there are clearly identifiable procedures that can be included, concurrent with or after data collection, to allow reasonable interpretation of the collected data. Dr. Fenske agreed with Dr. Brimijoin, but noted that rodent data often is extrapolated to humans using uncertainty factors. He agreed with Mr. Evans that there is minimal potential for breakthrough when WBD garments are concerned. The issue of concern is that exposed skin—face, neck, and hands—are significant contributors to total dermal exposure. He commended EPA for its focus on these important issues. Dr. Fenske did not recommend human hand wash efficiency studies but instead recommended that EPA apply uncertainty factors when necessary. If data indicates a significant discrepancy in exposure, hand wash studies can be performed after data are collected. He concluded that EPA has identified the main problems and proposed strategies to mitigate these problems. Further discussion of exposure analysis will be needed.

Dr. Brimijoin summarized that the use of passive dosimetry instead of biomonitoring is correct. The plans for this work generally are correct although certain details need to be

confirmed before final interpretation of the data. Dr. Chambers noted that issues of over-estimation and under-estimation of dose are compound specific. She commented that Dr. Popendorf had suggested effective and simple experiments that could help clarify recovery rates. She suggested that if the task forces can identify compounds whose doses are systematically underestimated, perhaps experiments with these compounds could be avoided and surrogates with the same active ingredient used instead.

Dr. Lehman-Mckeeman opened discussion of whether EPA has identified the relevant scientific and practical considerations affecting the choice of a sample selection strategy. She stated that the lack of biomonitoring is intellectually unsatisfying, but there is no easy answer to this question. EPA has not, however, characterized the limitations of the utility of the dataset if biomonitoring data is not collected. The Board must discuss whether or not to advocate biomonitoring and whether it can be performed in the context of these studies. She reiterated Dr. Chambers' comments that this work will use a group of surrogate chemicals. If biomonitoring of these chemicals appears technologically feasible and would provide usable data, it should be considered. Determining the appropriate analytical methods for a given compound and its kinetic properties will impact decisions on feasibility and will contribute to collection design. The abundance of a compound's metabolites, how many must be analyzed, and the ability to detect metabolites will also impact this decision.

Dr. Lehman-Mckeeman noted that there is the potential to generate a great deal of unusable data using biomonitoring. Additionally, biomonitoring will provide chemical-specific exposure information, but not use-specific information. Currently, biomonitoring is performed using rodents to gather initial data, which then is used to develop an implied dose for risk assessment; thus, excluding biomonitoring from task force protocols is consistent with current EPA risk assessment activities. She concluded that it is questionable whether biomonitoring would be feasible and generate useful, valid data. The idea of using biomonitoring to detect break-through is a minor issue.

Dr. Lebowitz expressed his concern about the lack of information on biomonitoring and metabolites for the compounds in question. He noted that pharmacokinetic/pharmacodynamic data is constantly being generated and may permit analysis of more compounds in the future. EPA could continue to pursue and gather this data. For a variety of reasons, in particular the contribution of multiple routes of exposure to total dose, measurement of whole body dermal and inhalation exposure would underestimate exposure and would not be scientifically reliable. Dr. Lebowitz stated that the goal of this work is to ensure exposures are minimized, but the protocols would underestimate aggregate and total exposure. Evaluation of data provided by AHETF comparing dermal dosimetry and biomonitoring indicates that biomonitoring detects higher total exposure levels, which may be chemical specific. Dr. Lebowitz concluded that the task forces have not addressed all the scientific considerations of biomonitoring.

Dr. Brimijoin clarified that Dr. Lebowitz suggested that in certain exposure scenarios, exposure by other than dermal routes could become important and thus using only dermal monitoring methods would seriously underestimate exposure, and that Dr. Lebowitz had suggested a focus on biomonitoring efforts to compare representative compounds in one set of workers amongst scenarios to develop corrections for the dosimetry data. Dr. Lebowitz

remarked that he had concluded that for surrogates for which metabolic and excretion data is available, a set of workers could participate in biomonitoring protocols sufficiently prior to and after exposure because dermal exposure usually contributes only a small fraction of total exposure to these compounds. By subtraction, an estimate for these surrogates could be developed and this would provide researchers with more accurate and reliable information on adsorption. Dr. Lebowitz advocated selective application of biomonitoring protocols.

Dr. Popendorf stated that his overall opinion was that biomonitoring was not needed and could result in unnecessary complications. The AHETF governing documents propose 10 chemicals. It is reasonable for the task forces to review the biomonitoring capabilities of those 10 chemicals and comment on the threshold and viability of performing biomonitoring as Dr. Lebowitz has described. Dr. Popendorf added that he was comfortable with the ability of passive dosimetry garments to prevent other routes of exposure, although face and hand exposure could allow some absorption. The compounds proposed have high thresholds for biomonitoring and probably will not be easily detected, particularly if passive dosimetry garments provide good interception. The number of chemicals examined will need to be reduced if biomonitoring is required and biomonitoring also would be limited to workers who did not have prior exposure to a chemical, resulting in selection bias of participants. Biomonitoring also will not help resolve issues related to uncertainty factors needed to determine exposure from a generic database. Dr. Popendorf concurred that further documentation of the 10 experimental chemicals is needed, but remained unconvinced that this would result in discovery of more viable options for biomonitoring.

Dr. Brimijoin concluded that the Board does not appear to be in favor of imposing biomonitoring across all protocols. Without biomonitoring, the data will still be valid; however, if biomonitoring could inform the data and if there are instances in which limited studies could be performed in parallel, the Board would consider recommending such studies. EPA could examine the surrogate chemical list and determine which have robust analytical methods and known kinetics and could be used in a biomonitoring study.

Mr. Jordan agreed with Dr. Lebowitz's observation that aggregate exposure occurs from many routes is correct; however, EPA data covering many chemicals shows that occupational exposure is significantly higher than that which occurs by other routes (such as through ingestion of food or water or exposure to residential pesticides). The goal of the task forces is to develop a generic database to use for estimating exposure for a wide variety of chemicals. Passive dosimetry allows EPA to identify the portion of the body in a given scenario that receives exposure. Methods to reduce risk usually involve specific protective equipment and this data would help inform decisions regarding the use of such equipment. Mr. Evans added that the break-through zone around a respirator will be monitored by a well-established method. Dr. Chambers agreed that these protocols seek to determine occupational worker exposure and thus disagreed with Dr. Lebowitz's call for biomonitoring, which would analyze exposure from food and other sources, not occupational exposure. She stated that she would prefer that extra resources be applied to fix variability and uncertainty related to passive dosimetry itself, rather than to biomonitoring. Dr. Fenske agreed with Dr. Chambers. The goal of this project is to assess dermal and inhalation exposure. Advising EPA to impose biomonitoring could be perceived as onerous by sponsors. He summarized that these are large, labor intensive studies, as

evidenced by the QA/QC parameters. Adding biomonitoring would result in a completely different study. He also noted that, despite his criticism of the Ross et al (2007) article, the article contains important information that the Board should consider. The article carefully culled information from many studies that seeks to address the issue Dr. Lebowitz raised. The article found 14 studies with sound biomonitoring and skin exposure measurements that contain information that could be useful to EPA. He concluded that biomonitoring was not an initial part of the proposal and he did not wish the Board to leave the impression that it was considering requiring biomonitoring.

Dr. Popendorf noted that the Ross article did show that correlation was better for average experimental values. This reinforces the idea that passive dosimetry, biomonitoring, and inhalation monitoring are comparable. He agreed that biomonitoring was not needed. Dr. Brimijoin summarized that passive dosimetry was favored. The Board would not recommend biomonitoring, but the Board report can include Dr. Lebowitz's reasons for including it. There is substantive evidence that the proposed methods are appropriate. Dr. Lebowitz stated that after hearing discussion from other reviewers, he declined to include his views about biomonitoring in the report.

QA/QC Controls

Dr. Lehman-Mckeeman opened discussion of the proposed QA/QC procedures by commenting on how the extensive number of procedures underscored the efforts to develop an appropriate infrastructure and noted that the SOPs create a new level of sophistication for this field of research. She commented that some information that should (but did not appear) in SOPs could be found in the governing documents, which indicates that these issues had been considered. She addressed the area of administration and noted that the SOPs in this area were reasonable, with the exception that specifics concerning the training of PIs and study observers were not clear. Study observers working in the field will make decisions concerning whether clothing dosimeters are worn correctly or whether a worker shows signs of heat-related illness. The relationship of study directors to other personnel needs clarification given that the study directors may not physically observe the study.

Concerning issues related to data quality and sample integrity and consistency, some of the SOPs provide less information than the governing documents. What constitutes a "good" sample is not clear in the SOP; for example, whether and how worker compliance with the protocol or variation in parameters such as airflow or temperature, would affect collection of data. Dr. Lehman-Mckeeman commented that spiking samples onsite to create analytical standards is a good approach, but clarification and description of the process is needed, because this will affect the quality of the results. She reiterated that the definition of a "good" sample and clarification of characteristics or changes that would disqualify a sample from the dataset is needed. She concluded that the SOPs were generally of high quality and will assure the quality of samples, with some minimal changes.

Dr. Fitzpatrick agreed that the SOPs were sound, but quite high in number. It will be difficult for study participants, including investigators, to remember these and thus procedures for assessing compliance (both intentional and unintentional) must be defined. The SOPs

indicate that scheduled inspections will be used to check for compliance; unscheduled inspections also should be considered. Dr. Fitzpatrick noted that the questions related to QA inspections are adequate for ensuring consent, determining that forms are signed and inclusion criteria followed; however, they do not provide a good assessment of the consent process. Observation of the consent process also creates difficulties because people may change their behaviors if they know they are being observed. Dr. Fitzpatrick concluded that training and re-training is the best way to ensure compliance. Inspectors should observe deviations from protocols and use this information to develop additional training needed to constantly improve the quality of the research. She also noted that casual conversations with investigators and study participants may reveal noncompliance without the need to ask about this specifically. Whistleblowers also can be a source of information concerning compliance. A reporting plan to facilitate whistleblowers confidentially contacting EPA or the governing organization should be developed.

Dr. Chambers agreed with Drs. Lehman-Mckeeman's and Fitzpatrick's assessment. She added that EPA can best judge whether all necessary issues have been addressed and considered that the task forces' desire to collect high quality data will help ensure compliance with appropriate standards.

Mr. Hamey questioned whether photographs could be included in reports. Dr. Fenske explained that photographs and videos could be included. Dr. Popendorf noted that the AHETF documentation assuming half of the LOQ as the LOD was unusual and recommended that they cite reasons for using this procedure; if this approach is not citable, the AHETF should use the approach described by the AEATF for this calculation.

Design of Scenario-Level Sampling

Mr. David Miller (EPA, OPP) presented EPA's design of scenario-level sampling strategies. He defined the target population considered during the design of scenario-level sampling strategies as the set of all possible handler-days in which scenario-specific tasks are performed. The protocols will involve approximately 1.1 million handlers and approximately 2 million handler days. Two approaches were considered for gathering probability samples—the simple random sample and the complex probability sample. Complex probability sampling is more typical for these types of projects. For example, National Health and Nutrition Examination Survey (NHANES) used complex probability sampling to sample a representative U.S. population. Complications associated with complex probability sampling include its high cost, the absence of a sampling frame, and issues related to selection bias. Selection bias is a particular issue for these protocols because the studies will only use volunteers, increasing chances of bias.

Because of these issues, the task forces have considered two alternative sampling strategies, purposive representative sampling and purposive diversity sampling (PDS). Purposive representative sampling captures a small sample of handler-days that is a "miniature" of the target population, with respect to important factors concerning range and extent of exposure. PDS captures a small sample of handler-days which are diverse with respect to factors related to range and extent of exposure. The task forces propose that PDS is more likely to

reflect a broad range of heterogeneous conditions than probability sampling. PDS can be diversified on the amount of active ingredient handled, the individual (MU), location and time, and other factors (such as equipment type, crops, rates, and micro-location). Site selection will emphasize more common conditions and the task forces will be required to provide rationale and/or justification for selection of sites or site conditions based on diversity criteria.

PDS permits a non-random sample to perform at least as well as a small, same-sized probability sample. It provides greater assurance of obtaining a sample that reflects a broad range of conditions and makes it less likely that high or low end exposure conditions would be missed. Augmenting scenario data with new clusters in the future will be straightforward, and conditions of interest will be easier to target. Experts including Drs. Leslie Kish and R. Whitmore contend that, in survey sampling, judgment is preferable to probability sampling unless the number of clusters exceed 10 to 20 and that a probability-based sample is not necessary if data for only a small sample (20 or fewer persons) can be collected for reasons of cost. In these cases, expert judgment and prior knowledge can be used to ensure that the sample units are representative.

Given this, it is acknowledged that PDS is not a probability-based sample and can only be used to establish a surrogate distribution of exposures. Surrogate distribution cannot be equated to actual distribution in a target population using pure statistical sampling theory; however, PDS can capture major aspects of an actual distribution. Results using this type of sample are not expected to be substantially different from those derived using a small, same-sized cluster random sample. PDS also is considered to be adequate for practical regulatory purposes.

The SAP has expressed concern with the proposed purposive nature of sample selection because PDS assumes underlying random selection can be used to estimate sample sizes. Appendix C of the SAP report provides discussion of potentials for bias and an alternative stratified approach. The SAP expressed concern that use of a non-probability sample would essentially preclude consideration of appropriate weighting to estimate distributional parameters including means, standard deviations, upper percentiles, etc. Thus, the SAP recommended an informal approach for identifying top factors and for assigning probability weights to approximate frequencies.

In response to the SAP, the task forces have attempted to address this concern given the constraints regarding available data and resources; EPA will evaluate the supporting data and documentation that will be submitted by the task forces to support their approach. However, given the unique aspects of this monitoring program and its relatively small size, OPP believes PDS is adequately representative of the target population and can be used to develop exposure assessments of occupational handler populations.

Statistical Justification of Number of Clusters and Monitoring Units

The number of clusters and MUs must permit collection of sufficient data for each handler scenario to meet specific minimum or ‘benchmark’ adequacy requirements. Sufficient data will permit calculation of the arithmetic mean, geometric mean, and 95th percentile of the normalized exposure distribution accurate to within K-fold of the true (underlying) parameters

with 95 percent confidence. To meet this objective, the task forces have proposed to collect data using a cluster approach. For this approach, groups of individuals within a location will be sampled using a nested design. Sampling multiple individuals within a given location can provide economies of scale and improve efficiency because individuals within a cluster tend to be more similar to each other than individuals in different clusters, given study effects such as protocols, study personnel, weather, etc. OPP agrees with the task forces' conclusion that cluster sampling is the most efficient way to obtain the necessary data and is more appropriate than other sampling designs.

The design must consider the number of clusters that must be sampled and the number of individuals in each cluster needed to generate an estimate of the arithmetic mean, geometric mean, and 95th percentile of the distribution that are within benchmark accuracy goal limits. This will depend on the Intra-class Correlation Coefficient (ICC), shape of the distribution, and the "spread" (variance) of the distribution. The K-factor is the ratio between the estimated parameter based on a sample and the true (or actual) factor as determined by simulation. Estimates of the geometric mean, arithmetic mean, and 95th percentile of an underlying log normal distribution should be within 3-fold of the true values at least 95 percent of the time.

The AHETF used simulations to create a table of K values that lists the corresponding number of clusters, number of individuals per cluster, and associated K value for each of a variety of assumed coefficient of variance (CV) and ICC values to help determine the number of clusters needed. The AHETF performed simulations using Monte-Carlo techniques to estimate values of K for the 95th percentile and arithmetic mean under various assumed conditions (ICC = 0.1, 0.2, 0.3, 0.4, 0.5 and CV = 1.5, 2.0, 2.4, 2.9, 3.5). For geometric mean, the AHETF used analytical solutions rather than simulations. Based on these approaches and the SAP's support of the task forces' general approach to estimating K values, OPP agrees with the use of K=3 as a reasonable benchmark accuracy objective.

Sensitivity analysis examined how ICC and CV affect K across various design configurations. K is relatively insensitive to ICC and CV in the selected five MUs in five clusters for one scenario design. It also was determined that there were no alternate configurations that provide practically equivalent K values that would reduce both cost and the number of individuals needed; some alternate configurations produced a similar K at substantially higher cost with fewer individuals.

Within-Worker Variability

Dr. Jonathan Cohen (ICF International) presented the AEATF's assessment of sampling approaches, cluster design, and optimal sample design. AEATF faces the same issue for its sampling approach as the AHETF. Stratified random sampling and probability sampling would be impractical and inefficient. Thus, the AEATF also will use a PDS approach.

Clusters are slightly different for the AEATF, because antimicrobial users work primarily indoors; thus, location and environment are expected to have minimal impact. Work also will occur under similar environmental conditions with respect to surface types, temperature, humidity, and air exchange rates. For the AEATF, a cluster includes a building (or complex), a

time period, and research staff and participants. Surrogates for confounding factors are room size, construction materials, loading levels (dirtiness), and research staff behavior differences.

There was no available data on an antimicrobial ICC; no appropriate studies with tests on multiple subjects at the same location/time period could be identified. The ICC is expected to be low, and given the average ICC of 0.3 from AHETF outdoor agricultural scenarios, the AEATF has decided to use an ICC of 0.3 as the upper bound for ICC for antimicrobial scenarios.

Four studies were used to estimate CV. These studies were Chemical Manufacturers Association studies on exposure by mopping, wiping, and aerosol, and a study on aerosol exposure from the PHED. A graph illustrating the distribution of normalized dermal exposure showed that the means were different, but within each study, the relative variability was approximately the same. The PHED study had a lower CV than the other three studies. Analysis of the pooled CV of the studies demonstrated that the relative variabilities were the same, and estimates for a pooled CV of 1.42 and a geometric standard deviation (GSD) of 2.86 were derived. The CV of 1.42 is lower than that of the AHETF CV of 2.4, as expected.

Issues similar to those considered by AHETF for sample design were considered for AEATF, namely the number of clusters and the number of individuals from each cluster that need to be sampled to obtain estimates of the arithmetic mean and 95th percentile of the distribution that are within K-fold of the true estimate, with 95 percent confidence. Using Monte-Carlo simulations, it was determined that an ICC of 0.3 and CV of 1.42 gave a K value of 3 when three clusters and six MUs per cluster were used.

The current occupational exposure approach used in the PHED estimates a single unit exposure from the PHED database for both single-day and multiple-day exposures; these are considered to be "central tendency" estimates and repeated measures (replicates) are "counted" as different (distinct) measures. For example, one person performing a task three times would be counted as three individuals. OPP recognizes that the distribution of single (one-time) measures on different people cannot directly be used to estimate distribution of long-term exposures and that within-worker and between-worker variance must be considered. Multiple measures on the same individual also cannot be treated as independent measurements and expected (day-to-day) correlation of measurements within individuals must also be considered.

OPP recognizes that distribution of single-day exposures can only be used to directly estimate single day exposures and long-term average (arithmetic mean) exposures. Distribution of single-day exposures can be used to estimate distribution of multiple-day average exposures if assumptions are made with respect to within-worker correlation (R_{ww}). If R_{ww} is 0, single-day distribution can be used for longer-term average exposures, and repeated independent samples should be drawn. This assumption underestimates long-term average exposures at the high end of the exposure distribution and overestimates low end exposure. If R_{ww} is 1, single-day distribution is equivalent to longer-term average exposure. A R_{ww} of 1 assumption overestimates long-term average exposures at the high end of the exposure distribution and underestimates the low end of the distribution. AHETF's preliminary literature search and available data suggests that R_{ww} will be approximately 0.5 to 0.9.

The majority of the SAP believed it was appropriate to de-emphasize within-worker variability (repeated measures) and instead use available resources to add clusters and increase sample size. The SAP noted that conducting repeated measurement would constrain the eligibility of handlers, and thus introduce selection bias. A minority of panel members believed that repeated measure would provide an opportunity to capture measures of R_{ww}.

Given the unique aspects of this monitoring program and its relatively small size, OPP concluded that PDS provides a sample that is adequately representative of the target population and can be used in developing assessments of exposure to occupational handler populations. OPP agrees with the task forces' conclusion that cluster sampling is the most efficient way to obtain the necessary data and is more appropriate than other sampling designs. OPP also believes it is appropriate to de-emphasize within-worker variability (repeated measures), and resources should be used to add clusters and increase sample size. Therefore, OPP will not require the task forces to perform repeated measurements to assess within-worker variability.

The HSRB was asked to determine whether EPA has identified the relevant scientific and practical considerations affecting the choice of a sample selection strategy. The Board also was asked to comment on its agreement, or disagreement, with EPA that the task forces should provide scenario-specific information about the availability of data to identify significant variables potentially influencing exposure and about the feasibility of developing a sampling strategy to address those variables quantitatively. The Board was asked whether EPA had appropriately characterized the limitations on the scientific usefulness of the resulting data attributable to the choice of the sampling strategy.

The HSRB also was asked to comment on any additional information needed by the Board to assess the adequacy of the justification for the number of clusters and MUs in specific AHETF and AEATF study proposals, and whether EPA had appropriately characterized any limitations on the scientific usefulness of a database that doe not include repeated measures.

Dr. Carriquiry questioned Mr. Miller how the 95 percent confidence interval was computed. Mr. Miller explained that he used layered regression and a mixed model. Dr. Kim stated that he had issues with the justification for non-probability sampling, especially the assertion of absence of frame and selection bias. In any survey, it is difficult to determine sampling frame, thus, absence of frame is not a good justification for non-probability sampling. Dr. Kim added that it is difficult to measure the accuracy of estimated parameters for both forms of sampling.

Public Comment

Dr. Larry Holden of Sielken and Associates Consulting, Inc.

Dr. Larry Holden (Sielken and Associates Consulting, Inc.) clarified that the purpose of using a surrogate distribution is to develop an estimate of sample size. Using non-probability sampling, convenient samples and numbers of samples are collected. The idea behind the approach detailed in the presentation was to use a surrogate model to develop a reasonable

sample and sample size. Clusters were used because previous studies showed that it was effective in avoiding the tendency to use a small sample.

PDS will be used to counteract the tendency to collect conditions that are too similar, and thus counteract the cluster effect. Because workers must volunteer to participate, it was believed that the sampling frame was not consistent with all possible risk. Dr. Holden referenced Appendix B of the SAP report and noted that given the small sample size and the accuracy desired, random sampling would not provide significantly better data. He acknowledged that it is possible to include the volunteer nature of the participants in the probability design, but the nature of recruiting may affect selection bias.

Board Discussion

Design of Scenario-Level Sampling

Dr. Fenske opened the Board discussion of the charge questions and acknowledged that the task forces had adequately explained the scientific and practical considerations of their study designs and demonstrated a solid understanding of the methodologies in question. He referenced the comparison of purposive representative sampling and PDS, noting that a problem is not knowing the characteristics of the handler days within a scenario, which will make developing a scaled model of this challenging. He continued that it was not clear who had decided which experimental factors were most important to consider. Dr. Fenske recommended that a broad range of the amount of active ingredient handled be included in a scenario. He added that the meaning of "diversify on an individual" also was unclear. Dr. Fenske agreed that location and time define a cluster, and that different types of clusters are needed, but there likely will not be many unique clusters and the criterion "different" is unclear, as is how "other" factors, such as crop and equipment type, will be weighed. Mr. Miller explained that the source of all the decisions presented at this meeting will be available in the protocol that will be presented to the Board in October 2007.

Dr. Fenske requested the meaning of "diversify on the individual." Mr. Miller replied that this was an attempt to recruit and analyze exposure for a broad range of individuals performing pesticide application, based on language, age, and experience. Dr. Fenske commented that the importance of these factors must be addressed. Mr. Miller confirmed that this would be discussed within the task forces and likely will be evident in the protocols.

Mr. Hamey stated that the practical and scientific issues had been well identified; however, he believed that the statement in the governing documents regarding the conclusion that PDS and purposive representative sampling will, because of the small sample size, describe the true distribution equally well, had not been resolved. He also speculated on the idea of diversity, commenting that in the United Kingdom, diversity should be based on farm size because this correlates with different sizes of equipment used, and different training procedures, behaviors, and application details.

Dr. Fenske continued that, unlike in the United Kingdom, U.S. workers do not need to be certified to apply pesticides and instead work under the supervision of a certified applicator.

There are important differences in training by a supervisor versus certification training. Any attempts at diversity should include an appropriate number of non-certified applicators.

Dr. Lebowitz referred to the AEATF governing document (page 70) and asked Dr. Cohen to comment on the discussion regarding quantification of the impact of ignoring clusters and treating data as a simple random sample. Dr. Cohen responded that he believed exposure estimates would be developed based on random sample assays, and then compared to estimates using clustering. Dr. Kim noted that any analysis should follow an established design. In this case, given a point estimate, the mean will be unbiased but variation could cause an anti-conservative estimate of the standard error. Dr. Cohen stated that, if AEATF clustering is too low, adding more variables could result in worse data than would be generated using a random sample. Mr. Miller added that the AEATF design indicates that ICC must be considered which can get complicated. The goal of the analysis was to determine if clustering made a difference, and if so, how much a difference. Dr. Popendorf noted that protocols will likely address clustering and it will likely have less of an effect than was described in the presentation.

Concerning the second charge question, Dr. Lebowitz began by stating that scenario-specific information is needed, including the identity of significant variables influencing exposure to active ingredients and statistical sampling strategies needed to meet the criteria of providing useful data. Information on the relationship between scenario-specific exposure and a representative scenario of the target population also would be useful. He noted that the AEATF will not analyze scenario data in terms of exposure collected characteristics that would differ between scenarios. The governing documents describe some of the relevant variables, but these are not characterized as causing significant or even mild effects on exposure. These include variables such as temperature, humidity, air flow rates, equipment, amount of chemical used, and dilution rates, as well as behavior of individual MUs (i.e., use of PPE, smoking, gum chewing, etc). The AEATF appears to be focusing on variables they consider essential and that would help delineate an exposure scenario.

Dr. Lebowitz continued, saying that variables for inclusion and exclusion criteria need to be recorded. The SOPs call for a description of measuring instruments and how they will be used, but are described in a generic way. In general, information on the characteristics of variables, how they are collected and used, and their handling, should be detailed in the governing documents or in an SOP. The task forces also presented information on known variability in previously collected data, which will help design the study and determine population size. Dr. Lebowitz concluded that the task forces should provide scenario-specific information to the Board.

Dr. Popendorf commented that the AHETF governing documents indicate that they will provide scenario-specific information, but he could not find whether AEATF would provide this information. Scenario-specific information can be a useful tool, as has been found for previous studies. For example, the amount handled may be the primary variable, but there are other parameters that also drive exposure. Standard field notes or standardized descriptions of good and bad practices may help to identify these parameters. The parameters then can be triaged on a subjective basis, based on observations; this may help determine which practices might lead to higher rates of exposure.

Dr. Lehman-Mckeeman agreed that the task forces should provide scenario-specific information to identify significant variables. Dr. Brimijoin summarized that Board agreed more information to identify significant variables was needed and asked for comments on ways to capture important variables.

Dr. Fenske questioned whether the Board's decision on this issue meant that EPA will ask the task forces to provide a ranking of critical parameters, based on expert judgment. A diversity of MUs is desirable, but decisions must be made concerning the importance of some variables (i.e., training, compared to others). He suggested that a point-by-point discussion of variable importance, with expert rationale, be held. Dr. Popendorf agreed, but stated that he was not sure this conversation should be required before field studies begin. Ranking of variables can be developed during the observation phase of the studies and field notes can be used to categorize exposures. This information could be entered into the database and would be useful for future analyses. Dr. Fenske countered that a structured list of variables to observe would be needed beforehand to collect this information through field notes. Dr. Lebowitz suggested that the Board should emphasize a need for both task forces to develop a set of questions and a checklist to be used to gather this data. Dr. Brimijoin noted that many potential variables influence exposure and concluded that as much effort as possible should be made to identify ahead of time the variables most likely to be important, and a checklist to use in the field should be developed.

Dr. Carriquiry opened discussion of the limitations of the scientific usefulness of the data attributable to the choice of sampling strategy. She disagreed that PDS was the best alternative for this work and stated that it was untrue that PDS gives better results than random sampling. PDS may be preferable for a unique group of people for which there is no sampling frame, but this is an easy sampling exercise. She commented that Mr. Miller's and Dr. Cohen's presentations implied that many factors impact exposure. If this is the case, she recommended that EPA not accept the assertion that a group of experts can identify all possible factors and determine the effect of this on the PDS approach.

Dr. Carriquiry noted that PDS may be useful in applied social science studies where the main objective is description; PDS is useful for qualitative, not quantitative analyses. PDS is inappropriate for quantitative studies because it is impossible to measure the error for a surrogate distribution. The surrogate distribution itself could be a good representative of the true exposure distribution or could be significantly different, and there is no way of checking assumptions when PDS is used.

Dr. Carriquiry addressed the sample size argument that PDS sometimes generates better results than random sampling if the sample is small and the "universe" also is very small and very well-known. In the case of the handler exposure studies, the "universe" is unknown, which completely negates the advantages of PDS. Sample sizes must be very small, on the order of eight to 10, before non-random sampling is preferable to random sampling.

Dr. Carriquiry suggested a way to use random sampling without greatly increasing the cost of the studies. She noted that the most expensive part of the studies is gathering dosimetry

data (approximately $20,000 per person per day) and also travel for study personnel. A compromise would be to systematically pick clusters or locations, which could be defined as counties, states, or contiguous counties. Within a location, a list of farms could be easily developed based on information from county extension offices, which have information on crop type, size, and location of the farms. The farms then would be stratified by size and crop type and then one to three farms within a strata picked randomly (depending on the number of observations in a cluster). After this, handlers at a farm would be randomly chosen. This would be a more defensible approach, especially if the data is intended for use for regulatory issues. She concluded that she supports the study, except for the use of PDS; however, this is an easy issue to correct and using the proper sampling approach will significantly improve the quality of the data.

Dr. Brimijoin stated that Dr. Carriquiry's analysis and suggestions would constitute the Board's recommendation in its report at this time.

Dr. Dallas Johnson (Consultant to the Board) agreed with Dr. Carriquiry concerning sampling. He noted that certain factors, such as amount of active ingredient handled, and equipment type can be controlled and would be part of the fixed effect side of the model. Factors, such as location, time, and crop type, are less controllable and thus fall on the random side of the model. Purposely picking factors on the fixed side of the model may be acceptable, but purposively picking from the random side is problematic. He agreed that there is no way to determine the confidence interval (CI) if PDS is used. Dr. Johnson speculated that if the variances and estimated standard errors from the data are overestimates of what would be determined using random sampling, PDS exposure estimates would be conservative because of the wider CIs.

Dr. Carriquiry agreed with Dr. Johnson on the issue of fixed effects and the number of factors. Some of these must be accounted for, but at some point factors must be sacrificed to avoid significantly increasing the sample size. The question is whether to poorly gather data for many scenarios or reduce the number of scenarios by one or two and focus more resources on generating sound data from the remaining scenarios. Good scenario data will allow extrapolation across multiple scenarios.

Dr. Chambers commented that scenarios constitute different activities, so caution should be taken in reducing the number of scenarios. She asked whether the design of five MUs in a cluster, and five clusters per scenario changed Dr. Carriquiry's conclusions regarding PDS versus random sampling. Dr. Carriquiry responded that her conclusions would not change because the relevant sample number for a scenario is 25, which is large enough to justify random sampling.

Dr. Popendorf presented graphs depicting the differences in the two sampling approaches. The K value is driven by EPA and its approach that it will be consistent with the amount of substance handled. He assumed that EPA has found this to be a successful approach from a regulatory perspective. If a log normal distribution is examined on a log scale, the distribution becomes normal. If this graph represented the amount handled, the distribution would appear normally distributed and mean and variation could be determined. The purpose of PDS is to

predefine categories (i.e., amount handled) and then try to equalize this across categories, which could generate an acceptable mean; however, the standard deviation and 95th percentile values will be in error if the amount handled is not a primary driver of the distribution. This would have implications for use of this data for regulatory purposes. Dr. Carriquiry agreed with this analysis. Mr. Miller agreed with the comments and that PDS is controversial.

Mr. Miller requested clarification of the random sampling strategy described by Dr. Carriquiry. He explained that needing to include handling of a certain amount and certain chemical in a given scenario had played a role in the decision to use PDS. Dr. Carriquiry explained that a compromise between random and purposive sampling can be reached. Locations can be picked systematically (or purposively) to have defined information on the types of crops and size of the farm. Within a location, a more random approach to sampling could be used. Issues, such as chemical identity and handled amount, are correlated with characteristics of the location (i.e., large producers use different types of equipment than smaller growers and also may use different application procedures or chemical types). Although it may require more legwork to determine these parameters, several Board members noted that this information should be easily available from extension offices or clearinghouses.

Dr. Kim commented that the unwillingness of the sponsors to create a sampling frame is problematic. Scenarios will dictate the sampling frame. He stated that this issue needs to be considered or it will be difficult to draw meaningful conclusions from the study. Dr. Brimijoin concluded that the Board believed a random sampling approach, in whole or in part, would provide better data.

Statistical Justification of the Number of Clusters

Dr. Kim opened discussion of the statistical justification of the number of clusters. If the assumption is that the surrogate sample represents probability sampling, the sampling described in the governing documents is adequate and the documents also provide a thorough discussion of the justification for the number of clusters and MUs based on sensible assumptions. Especially for the AHETF, the design of five MUs per cluster and five clusters per scenario is justified because of the analysis performed using existing data from the PHED, ICC development, and sensitivity analysis to determine the influence of clustering. He commended the AHETF's mathematical derivation of sample size, rather than basing sample size on traditional approaches. He noted that the AEATF also provided good justification of the design of three clusters with six MUs per cluster based on a GSD of 2.4 and an ICC of 0.3. His only caveat was to caution the task forces to be attentive to specific conditions that may require scenario-specific adjustments. He concluded that the cluster design was justified, but agreed that use of PDS was problematic.

Dr. Fenske argued that although the task forces believe they can identify and rank risk factors in terms of their impact on exposure and apply this to the study to get an appropriate distribution of exposure, there is no way to prove if the results of this exercise are correct. He stated that although it is appropriate for task forces to trust in their own knowledge base to rank risk factors, there is no way to determine whether a truly representative miniature sample has been created. He recommended that EPA seriously investigate the feasibility of random

sampling within a defined sample frame. He noted that Dr. Carriquiry had described a feasible and practical plan for doing this.

Dr. Fenske concluded that field studies are similar to epidemiological studies in that there is little control over conditions. He suggested that each study chose one goal around which they optimize what is controllable. He cautioned against weakening the design developed to achieve the primary objective in hopes of addressing a secondary objective. The planned AHETF and AEATF activities include a survey that will create usable exposure distributions for a number of scenarios. The numbers will be used to inform risk assessment activities for many chemicals and scenarios. Attempts to answer questions concerning amounts handled by changing or restricting the study design will require assumptions that a sufficient range of active ingredient handled can be examined. He recommended optimizing the representativeness of scenario data to optimize exposure, and agreed that random sampling would be preferable.

Dr. Johnson agreed with Drs. Fenske and Kim. He stated that the AHETF had provided sound justification of its five clusters with five MUs design and commended the sensitivity analysis. Based on this, Dr. Johnson concluded that he would not include more than five MUs per cluster, but instead would increase the numbers of clusters to reach 25 MUs per scenario. Dr. Johnson was less pleased with the AEATF's design of six MUs in each of three clusters, stating that five or more clusters would be better. AEATF should consider changing its study design in this manner.

Dr. Kim recommended that in terms of the numbers of clusters needed for the AEATF, as data accumulates in the database, a better estimate of ICC could be developed. Dr. Cohen clarified that an ICC of 0.3 was considered the upper bound estimate. If the ICC is as low as 0, the K value will be 2, which is better. It is true that in the document, the idea is to use three clusters as a default; once data is available to estimate a new ICC, cluster design can be re-visited. In response to a question from Dr. Johnson, Dr. Cohen clarified that the CV had been derived from data from four existing studies, but there was no data to support derivation of the ICC.

Dr. Lebowitz inquired why a cluster design was needed for AEATF studies. Mr. Miller replied that the original suggestion from the AEATF was to monitor more individuals in one location. EPA objected to this for fear of being unable to obtain information on the ICC. This led to the development of the three MUs per each of six clusters design. Dr. Carriquiry noted that there was an expectation of less between-cluster variability in the AEATF than in the AHETF. The different numbers of clusters responds to this, and thus use of fewer clusters in the AEATF design is justifiable. Dr. Johnson commented that estimating variance using only three clusters was somewhat weak. Depending on the cost, increasing the number of clusters would be optimal. Dr. Brimijoin concluded that the cluster size of three was acceptable to the Board and noted Dr. Johnson's disagreement.

Within-Worker Variability

Dr. Carriquiry opened discussion of within-worker variability. She noted that she would like to recommend replicates, because these can be used to estimate within-person variance relative to between-worker variance and exposure and gives a better estimate of the usual daily exposure of workers in a scenario. However, another way to determine within-worker variability is to gather replicate measures of a sub-sample of the same workers and averaging this value over all workers. This approach was used by NHANES in a survey to gather replicate measurements of a food intake in a sub-sample of survey respondents. If replicate measures are not taken, the tails of the exposure distribution may extend too far. If only one day's exposure distribution is used to determine the 95th percentile level of exposure, this estimate will be too high. This would actually be protective of workers because it will overestimate exposure and perhaps trigger stricter protective regulations. In this case, the main exposure estimates will be accurate with or without replicates.

Dr. Carriquiry acknowledged that this issue was recognized in the SAP report. The report proposes to borrow information from another source, assume a certain within-worker variability, and correct the distribution using external estimates of variance. It is permissible to do this, but extra estimates of within-worker variability must be chosen carefully because they can have a significant impact on the tails of the distribution. In the absence of replicates, EPA should be conservative and use 1-day exposure without correction as the true 10-day exposure, even though this results in overestimation of the distribution at the tails. EPA has recognized this problem and it is not a significant limitation. Errors can be easily estimated in the absence of replicate measures. Dr. Fenske suggested using data from PHED, which has many repeated measures performed on the same work force and could be used to inform variability issues for which there are no samples in the AHETF database.

Dr. Johnson agreed that if the choice is between including many workers with one measure each or few workers with many measures, EPA should opt for many workers with one measurement. This does not place limits on the database, although the ability to separate within-worker and between-worker variance is lost.

Dr. Lebowitz inquired if within-subject variability would contribute to the ability to generalize the exposure estimates made from the data. Dr. Carriquiry responded that under the given resource constraints, a limited total number of observations can be made. If it were possible to have a larger sample size, replicates of some workers would provide uncertainties between estimates. In this case, the estimate of the 95th percentile will be biased because of having only one observation per worker, but this could be corrected using external information.

In response to questions from Mr. Miller, Dr. Carriquiry clarified that EPA was interested in the distribution representative of one day's observations. Given one observation per worker, the ideal approach would be to have every worker observed over many days, and then take the average of these observations to determine the distribution. She continued by reiterating that the estimates at the tails of the distribution will be too long because of additional noise that cannot be eliminated without replicates; thus, estimates at the 95th percentile of exposure will be higher

than the true exposure. The overall result of this will be protective of workers, and estimates at the center of the distribution will not be biased. Dr. Popendorf noted that slide 47 of the Agency's presentation described this effect.

Mr. Jordan clarified that EPA performs several types of risk assessment for worker exposure including 1-day risk (exposure in a single day of work) and short-intermediate term risk (4 to 5 days to 3 to 4 weeks of exposure). The value used for exposure components can differ between these two levels of exposure because over multiple days, an individual handler will receive more or less exposure, based on his activities. Without data to characterize within-worker variability, use of a single day's exposure data will overstate the multiple day risk and the 95th percentile of exposures for multiple days will be greater than that of one day. The 95^{th} percentile of a single day measured by the task forces will correspond to the 95th percentile of 1-day exposures. Without repeated measures, EPA acknowledges that measures of multiple-day exposure cannot be developed without making some adjustments.

Dr. Johnson noted that the measure of 1-day exposure should include both between-worker and within-worker variation. An advantage of having repeated measures is that the two components can be estimated and parameter estimates that depend on the variance of these components can be made. Dr. Carriquiry noted that for the distribution sought by EPA, within-worker variance is noise and between-worker variance is needed. There are external sources of information to measure within-worker variance (i.e., PHED data).

Subject Recruitment and Enrollment

Introduction

Mr. Carley presented EPA's evaluation of subject recruitment and enrollment issues. His presentation focused on the AHETF monitoring program, which is expected to be more complicated than that of the AEATF. The AHETF recruiting process begins with recruitment of cooperating growers or landowners (hereafter known as cooperators). Potential cooperators are identified; screening and selection begins after final protocol approval. Any proposed deviations from the final protocol must be justified. After this, cooperators identify a potential worker pool. The Study Director (SD) presents the proposed research to the workers as a group and then seeks informed consent from individual workers.

Mr. Carley provided detail on the grower recruitment process. Scenario designs specify the needed characteristics of a cluster. Based on this, the Local Site Coordinator (LSC) suggests potential sites and cooperators to the SD. The LSC also identifies needed equipment and may be involved in the management of samples, although this is under consideration. The SD develops the protocol without final identification of the site(s). The protocol is then reviewed (i.e., by IRB, CDPR, EPA, and HSRB), and after revision and final approval of the protocol by the IRB, the LSC recruits potential cooperating growers. The SD meets with potential cooperators to determine that the grower meets the requirements specified in the scenario design (i.e., appropriate crop, equipment, skilled workers, and use of surrogate chemicals), agrees to allow research on his/her property, promises access to workers for recruitment, and promises not to

influence workers' decisions. Based on these criteria, the SD selects the study cooperator(s) and adds any needed specifications to the protocol.

To recruit workers, the SD meets with workers as a group; the grower will not attend this meeting. The SD explains the research to the workers and provides IRB-approved recruitment materials. The SD also may show IRB-approved videos illustrating the study procedures and use of dosimeters. After soliciting expressions of interest by individual workers, the SD meets individually with interested candidates to review informed consent documents, answer any questions, and solicit consent to participate. Because the SDs are primarily English-speaking and many of the workers are expected to primarily speak Spanish, the assistance of bilingual workers may be needed.

Preliminary EPA concerns include whether the study risks and benefits can be fully assessed without knowing where a study will be conducted; some study sites may employ a Spanish-speaking population of workers, so it will be difficult to judge if the informed consent process is adequate. Also, although EPA has been promised study-specific recruiting plans, the Agency questions whether such plans can be developed before cooperators are finally identified.

EPA's overarching concerns in recruiting, screening, and obtaining consent include ensuring equitable subject selection, fully informed and voluntary choice, and respect for subjects. Equitable subject selection must ensure representativeness, which hinges on the scenario-level design and the choice of appropriate clusters and cooperators. The Agency considers the lists of appropriate inclusion/exclusion factors (i.e., over 18 years of age, in good health, not nursing or pregnant, and of normal intelligence to be appropriate). The exclusion factors also include those who habitually wear more than the typical PPE (these workers would not be representative of the general worker population) and also LSCs and employees of the SD. One area in which EPA foresees difficulties is the exclusion of parties with an interest in the research. The Agency may call for more extensive exclusion in this regard for a particular study because of possible undue interest in the data or influence on other subjects.

The involvement of vulnerable populations in this research also is a concern of EPA. Several vulnerable populations have been defined intask force governing documents. Language proficiency and dependent relationships with the growers/employers are areas of specific concern. To help mitigate these issues, the recruiting strategy will be defined for each with input from the community. Study personnel are encouraged to develop ties to the community to help develop the recruiting strategy.

Fully informed choice requires the capacity to make decisions; the SD will assess this in the informed consent interview. The recruitment process has been designed with the assumption that English and Spanish will be the main languages spoken by workers. If the worker speaks only Spanish, a translation of the ICF performed by the Western IRB will be given to the worker, and an interpreter will be provided if the SD speaks only English. Literacy also is expected to be an issue. If a worker is illiterate, the ICFs will be read to him and a witness will be required. An interpreter will be needed if the worker speaks only Spanish and the SD only English; a witness also will be needed if the worker also is illiterate in Spanish. The interpreter in this situation could be an employee of the grower or a person chosen by the subject. The SD must be certain

that the interpreter can provide an adequate description of the research and ICF. The interpreter is not considered to be part of the research team and will not sign the ICF. The witnesses must be fluent in the language in which the informed consent discussion takes place.

EPA has concerns that the processes for English-speaking and Spanish-speaking workers are not equivalent. Depending on the language(s) spoken by the SD and the worker, two or three parties may be involved in the informed consent process. The presence of an interpreter may inhibit workers from asking questions. In addition, the interpreter may not understand the research well enough to translate accurately, and it would be difficult for a non-Spanish speaking SD to determine this. The SD also will be unable to confirm worker understanding. The ability of study observers to communicate with workers also will be impaired by language differences.

The complexity of the consent materials also presents a challenge. The AEATF wipe protocol informed consent was provided to Board members as an example containing all required elements in an accessible form and language. A description of the development of these materials is provided in the governing documents because preparation of appropriate consent materials is an essential element of the study-specific recruiting plan and different processes have been proposed for different languages. The wipe protocol also provides an example of how risks and benefits will be communicated. Confirming the subject's full and complete understanding of the protocol and risks and benefits is the responsibility of the SD, which will be difficult if the worker speaks only Spanish.

Fully voluntary choice also will require management of dependent relationships; the nature of the relationships between workers and growers will be site specific. Cooperators must promise not to influence workers and employees of interested entities will be excluded. To minimize peer pressure, no specific discussion of informed consent will occur until a worker expresses interest. Informed consent discussions will be held in private, and pregnancy tests and discussions of results also will be held privately. Real alternatives to cooperation will be provided by growers and explained by informed consent documents.

An AHETF Employer Promise has been developed. This promise calls for the employer to allow AHETF to recruit any employees with applicable training and experience in the tasks involved in the study, as determined by the SD. The employer acknowledges possible benefits, but promises to neither encourage or discourage employees to participate in the study, and promises that an employee's decision to participate, not to participate, or to withdraw from participation in the study will have no impact on his/her employment status or pay. Employees who decide not to participate, who withdraw from participation, or who complete participation in less than a typical work shift will be offered alternative work at their usual pay to complete their usual work shift and employees will receive their normal pay for days they participate in the study. Mr. Carley acknowledged that this promise had been thoughtfully developed and covered most of his concerns. He expressed some concern that field investigators may need to be more involved in recruitment and consent processes to alleviate some of the responsibilities of the SD.

Mr. Carley described the AEATF consent process, which contains two "fundamentally different" paradigms compared to the AHETF. The studies performed under the AEATF will be conducted either at an active worksite, which will require supervisor agreement similar to that

described for the AHETF and will require interested workers to meet with the SD at the workplace, or will recruit subjects to work at a site not under their supervisor's control. In this case, flyers will be posted at workplaces and interested workers will be instructed to contact the Field Coordinator by telephone. An IRB-approved script will be used to explain the study and confirm workers' interest; interested workers will then meet with the SD at the SD's office.

As part of respect for subjects, incentive payments ($20 for participating in an informed consent interview and $80 for beginning exposure monitoring) have been proposed. These fees are subject to refinement based on community input. To ensure privacy and confidentiality, no records of candidates who do not qualify or consent to participate will be kept, data will be collected by subject code, linkage of names and addresses to subject codes will be securely maintained, and subjects will not be identified in reports or in databases. Given the potential benefit of providing feedback on work habits and exposure to subjects, if a subject is interested in his or her own data, they should be provided with the data. The task forces have been encouraged to incorporate a description of this process in the SOP governing privacy of subject identity.

The Board was asked to consider whether the governing documents and associated SOPs of the AHETF and AEATF research programs included comprehensive and appropriate protections for human subjects of the research and, if not, to describe overlooked issues. The handling of language differences was specified as an area requiring further refinement and the Board was asked to determine whether EPA has overlooked any other areas in need of revision.

Public Comments

Dr. Brimijoin invited oral public comment on subject recruitment and enrollment issues. No oral public comments were received.

Board Discussion

Dr. Menikoff opened the discussion and complimented AHETF and EPA for their thorough review of the recruiting process and incorporating Board suggestions from previous meetings into the process. He agreed with Mr. Carley that only relatively minor refinements are needed. Given the vulnerability of the subjects, the involvement of worker representatives could be emphasized more strongly. Including subject advocates and representatives will strengthen protection for workers and the governing documents should include a discussion of this issue. Dr. Menikoff advised the task forces to consider the readability of consent materials, because many potential subjects may have low literacy.

Dr. Chadwick noted that the AEATF documents describing the review process had a table of contents that listed specific chapters describing sampling, subject recruitment, and IRB review, but the pages in the document read, "left intentionally blank." He found details on these issues in Chapter 2 and thus advised AEATF to change "left intentionally blank" to "described in Chapter 2." He also complimented the task forces on their efforts and inclusion of recommendations from HSRB and other agencies.

Dr. Chadwick specifically mentioned the age limit placed on pregnancy testing (50 years) in the AEATF documents and recommended that an exclusion based on menopause would be more appropriate than an age-based exclusion. AEATF also could consider testing all women, which is the plan of the AHETF. Dr. Chadwick also asked that the documents describe more completely how documents, such as those related to pregnancy testing, would be destroyed (i.e., shredded) to protect privacy.

Dr. Chadwick requested clarification on language issues. For example, AEATF states that if more than 15 percent of the sample is non-English speaking, translated documents will be provided. AHETF offers to provide all documents in English and Spanish; this is the better approach. Other Agency guidelines require that ICFs be presented in the potential subjects' native language. Regarding witnesses and interpreters, Dr. Chadwick recommended that witnesses not serve as interpreters and cautioned the task forces to be aware of the qualifications of the interpreters. He agreed that including more bilingual study investigators would be valuable.

Dr. Sharp complimented the task forces on the documents. He noted that when specific studies are reviewed, a recurrent theme will be protecting workers from undue influence by growers. Although this is mentioned, the task forces should have a management plan in place for each study that will ensure workers' right to decline to participate in the study. For example, if a grower has 50 workers who are all eligible to participate, perhaps only 25 of the 50 would be selected to participate, without revealing to the grower which workers wished to participate but were not selected and which workers declined to participate.

Concerning the translation processes, Dr. Sharp noted that the task forces proposed that materials be translated by the IRB, but speculated that more materials will likely need to be translated than an IRB may be willing to translate. Dr. Chadwick informed Dr. Sharp that Western IRB specifically provides a translation service. Dr. Sharp continued with his discussion of language issues and commended the task forces on their thorough discussion of these issues. He stated that ensuring that all volunteers have access to all documents (ICFs, pamphlets, etc.) in both English and Spanish is important. He agreed with Mr. Carley on the need to employ bilingual study staff. Volunteers may have questions both before and after undergoing the informed consent process and there will be a continuing need for bilingual staff during the course of the study. Dr. Sharp expressed concern about the phrase "translators of convenience," which could mean co-workers or family members. Using such translators is discouraged in clinical research because these people are unlikely to be familiar enough with the research to properly inform the subject. Dr. Sharp was supportive of the task forces' plan to include an impartial third-party witness for subjects who are unable to read. A clarification of the procedures used to recruit such witnesses is needed; Dr. Sharp noted that it would be inappropriate for the translators to also serve as witnesses. Another option is to hire dedicated consent monitors or research subject advocates who are specifically trained to determine whether consent is fully voluntary. Dr. Sharp also recalled Dr. Fenske's comment concerning the likelihood of encountering workers who speak languages other than Spanish or English and suggested that EPA consider if it would be appropriate to restrict eligibility to only English and/or Spanish speakers, unless this would introduce bias.

Dr. Fitzpatrick agreed that the potential for bias needs to be addressed if EPA considers restricting the studies to only English and/or Spanish speakers. She supported EPA's proposal to employ Spanish-speaking investigators to assist with consent processes. She inquired how the task forces would perform QA on consent processes that include interpreters, since the interpreters do not sign the ICF, thus there would be no evidence of use of an interpreter. She suggested that EPA ask for a certified translation (translation forward and back to the original language of the document) to ensure accuracy.

Dr. Fitzpatrick addressed the medical compensation, noting that the task forces agreed to compensate for reasonable medical costs if subjects do not have insurance. She stated that "reasonable medical costs" need to be defined more specifically, for example, do these include initial treatment, long-term care, or missed days of work. She also noted that subjects self-report their levels of health—most people tend to report themselves as healthy—and asked how the task forces would handle injury that occurred because of an unreported health condition.
Dr. Fitzpatrick acknowledged the task forces' plans for adverse event reporting and inquired how decisions to modify ICFs would be made if new risks are identified as a result of adverse event reporting. She added that ICFs also should inform subjects that if new information related to risk arises as a result of the study; subjects will be given this information so they can re-evaluate their consent to participate. She commented that if the task forces plan to permit subjects access to their own data, the task forces also must provide assistance with interpretation of the data.
Dr. Fitzpatrick concluded by noting that subjects will be asked to show a driver's license or workers card to prove immigration status and asked if the task forces have plans in place to protect the privacy of illegal workers. She also asked, while acknowledging that EPA has no control over this request, why California requested review of the studies by the Florida IRB.

Mr. Carley clarified for Dr. Fitzpatrick that because these are largely one-day studies, the issue of withdrawing consent because of adverse events is minor. Dr. Fitzpatrick requested task force response to this matter if an adverse event potentially affecting participation occurred at another site. Mr. Carley considered this to be unlikely.

Dr. Popendorf noted that the records of subjects who decline to participate are destroyed, but said that this data may be useful for populating a distribution of conditions if a random sampling approach is used. He expressed concern that if EPA continues with its proposed PDS approach, future users of the database may not be aware of this and may assume a random sampling approach was used; to prevent this, the database should contain a statement indicating that PDS was used. Dr. Carriquiry remarked that she believed EPA will adopt a randomized sampling strategy, which also will help protect workers from coercion. A list of possible workers would be provided to investigators, but the grower will not know which workers were selected or which declined to participate.

Dr. Brimijoin summarized that the Board was impressed with the consideration of the recruitment process and complimented the level of detail and careful thinking. He stated that it is likely these studies will achieve a high standard of scientific and ethical performance. Board members described some areas for improvement, including involving worker representatives early in the recruitment process and describing this in the governing documents; reconsideration of privacy protection and exclusion factors for pregnancy tests; ways to manage and reduce

potential grower influence on subject participation; attention to language issues and Board endorsement of the plan to involve bilingual investigators with appropriate knowledge and expertise; technical points concerning relying on translators of convenience; identification of appropriate witnesses; clarification of covered medical costs in case of adverse events; issues of confidentiality for illegal workers; and plans for ICFs to alert subjects to newly discovered risks.

Dr. Lewis thanked Dr. Brimijoin for serving as chair of this meeting. He also thanked the Board members for their efforts and his EPA colleagues for their preparation and the presentations given at this meeting. He stated that a *Federal Register* notice will be published to inform the public about the availability of the Board's report for this meeting. Dr. Lewis also stated that review of the April 2007 report would be conducted by teleconference and that a *Federal Register* notice would be published to inform the public of this event.

Dr. Brimijoin 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:

William S. Brimijoin, Ph.D.
Vice 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

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
Rochester, NY

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
Department of Environmental and Occupational Health Sciences
University of Washington

Seattle, WA

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

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

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

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

Michael D. Lebowitz, Ph.D.
Research Professor of Medicine & Epidemiology/Public Health
University of Arizona
Tucson, AZ

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

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

Sean M. Philpott, Ph.D., M.Bioethics

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
**Served as Chair at meeting

Attachment B
Federal Register Notice Announcing Meeting

Human Studies Review Board; Notice of Public Meeting

[Federal Register: June 6, 2007 (Volume 72, Number 108)]
[Notices]
[Page 31323-31325]
From the Federal Register Online via GPO Access [wais.access.gpo.gov]
[DOCID:E7-10859]

ENVIRONMENTAL PROTECTION AGENCY
[EPA-HQ-ORD-2007-0403; FRL-8322-7]

Human Studies Review Board; Notice of Public Meeting

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

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

DATES: The public meeting will be held from June 27-June 29, 2007 approximately 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-2007-0403, by one of the following methods:

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

E-mail: ORD.Docket@epa.gov.

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

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

Instructions: Direct your comments to Docket ID No. EPA-HQ-ORD-2007-0403. 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.

[[Page 31324]]

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 AM to 4:30 PM EST, Monday through Friday, excluding Federal holidays. Please call (202) 566-1744 or email the ORD Docket at ord.docket@epa.gov for instructions. Updates to Public Reading Room access are available on the Web site (http://www.epa.gov/epahome/dockets.htm).

EPA's position paper(s), charge/questions to the HSRB, and the meeting agenda will be available by early June 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-2007-0403 in the subject line on the first page of your request.

a. Oral comments. Requests to present oral comments will be accepted up to June 20, 2007. To the extent that time permits, interested persons who have not pre-registered may be permitted by the Chair of the HSRB to present oral comments at the meeting. Each individual or group wishing to make brief oral comments to the HSRB is strongly advised to submit their request (preferably via email) to the person listed under FOR FURTHER INFORMATION CONTACT no later than noon, Eastern Time, June 20, 2007 in order to be included on the meeting agenda and to provide sufficient time for the HSRB Chair and HSRB Designated Federal Officer (DFO) to review the agenda to provide an appropriate public comment period. The request should identify the name of the individual making the presentation, the organization (if any) the individual will represent, and any requirements for audiovisual equipment (e.g., overhead projector, LCD projector, chalkboard). Oral comments before

the HSRB are limited to five minutes per individual or organization. Please note that this limit applies to the cumulative time used by all individuals appearing either as part of, or on behalf of an organization. While it is our intent to hear a full range of oral comments on the science and ethics issues under discussion, it is not our intent to permit organizations to expand these time limitations by having numerous individuals sign up separately to speak on their behalf. If additional time is available, there may be flexibility in time for public comments. Each speaker should bring 25 copies of his or her comments and presentation slides for distribution to the HSRB at the meeting.

b. Written comments. Although you may submit written comments at any time, for the HSRB to have the best opportunity to review and consider your comments as it deliberates on its report, you should submit your comments at least five business days prior to the beginning of the meeting. If you submit comments after this date, those comments will be provided to the Board members, but you should recognize that the Board members may not have adequate time to consider those comments prior to making a decision. Thus, if you plan to submit written comments, the Agency strongly encourages you to submit such comments no later than noon, Eastern Time, June 20, 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.

The June 27-29, 2007 meeting of the Human Studies Review Board will address scientific and ethical issues surrounding:

• A research proposal from Carroll-Loye Biological Research to evaluate the efficacy of two conditionally registered products containing picaridin in repelling mosquitoes in the field.

• A research proposal from Insect Control & Research, Inc. to evaluate the efficacy of two unregistered products containing picaridin in repelling mosquitoes in the field.

• A completed study measuring the effects on human subjects of acute inhalation exposure to acrolein. Acrolein is an active ingredient used in biocides in agricultural and industrial water supply systems and is currently undergoing reregistration.

• Three completed clinical studies of the efficacy and side effects of 4-aminopyridine when used as a therapeutic agent to treat neurological

[[Page 31325]]

Symptoms in patients with either spinal cord injury or multiple sclerosis, 4-aminopyridine is an active ingredient used in bird repellents that is currently undergoing reregistration.

• Extensive background materials concerning research to quantify the level of exposure received by people who mix, load, and apply pesticides. These materials, which were prepared by the Agricultural Handlers Exposure Task Force and by the Antimicrobial Exposure Assessment Task Force, generally explain the scope of the research programs being proposed by the Task Forces and describe the general scientific framework for conducting the research. In addition, each Task Force has provided Standard Operating Procedures which will guide the conduct of the studies.

The Board may also be reviewing draft HSRB reports for subsequent Board approval. 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: May 31, 2007.

Kevin Teichman,

Acting EPA Science Advisor

[FR Doc. E7-10859 Filed 6-6-07; 8:45 am]
BILLING CODE 6560-50-P

Attachment C

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

June 27-29, 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-2007-0403

BOARD REVIEW OF ITS DRAFT APRIL 18-20, 2007 HSRB MEETING REPORT, ORIGINALLY SCHEDULED AT THE BEGINNING OF THIS MEETING, MAY BE RESCHEDULED EITHER LATER DURING THE MEETING OR AT A SUBSEQUENT TELECONFERENCE. IN ADDITION, TODAY'S MEETING MAY START EARLIER THAN LISTED ON THE AGENDA*

Wednesday, June 27, 2007

11:30 a.m. **Convene Meeting and Identification of Board Members**
William Brimijoin, Ph.D. (HSRB Vice Chair)
11:40 a.m. **Welcome**
George Gray, Ph.D. (EPA Science Advisor)
11:50 a.m. **Opening Remarks**
Debbie Edwards, Ph.D. (Director, Office of Pesticide Programs, [OPP])
12:00 p.m. **Meeting Administrative Procedures**
Paul Lewis, Ph.D. (Designated Federal Officer [DFO], HSRB, OSA, EPA)
12:05 p.m. **EPA Follow-up on HSRB Recommendations**
Mr. William Jordan (OPP, EPA)

Carroll-Loye Picaridin Mosquito Repellency Protocol LNX-001

12:15 p.m. **Science and Ethics of Carroll-Loye Protocol**
Mr. Kevin Sweeney (OPP, EPA) and Mr. John Carley (OPP, EPA)
1:00 p.m. **Lunch**
2:00 p.m. **Public Comments**
2:30 p.m. **Board Discussion**

a. If the proposed research described in Protocol LNX-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 LNX-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?

ICR Picaridin Mosquito Repellency Protocol

3:30 p.m. **Science and Ethics of ICR Protocol**
Mr. Kevin Sweeney (OPP, EPA) and Mr. John Carley (OPP, EPA)
4:15 p.m. **Public Comments**
4:45 p.m. **Break**
5:15 p.m. **Board Discussion**

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

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

6:15 p.m. **Adjournment**

<u>Thursday, June 28, 2007</u>

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

Acrolein

8:50 a.m. **Acrolein**
Abdallah Khasawinah, Ph.D. (OPP, EPA) and Mr. John Carley (OPP, EPA)
9:45 a.m. **Public Comments**
10:15 a.m. **Break**
10:30 a.m. **Board Discussion**

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

b. Please comment on the following:

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

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

4-Amino Pyridine

11:30 a.m. **4-Amino Pyridine**
Abdallah Khasawinah, Ph.D. (OPP, EPA) and Mr. John Carley (OPP, EPA)

12:15 p.m. **Public Comments**

12:30 p.m. **Lunch**

1:30 p.m. **Board Discussion**

a. The Agency's weight-of-evidence (WOE) document for 4-aminopyridine describes the study design and results of three clinical trials (**Grijalva et al. 2003, Segal et al. 1999, and Van Diemen et al. 1993)**. The WOE document also discusses the Agency's conclusion that these studies provide sufficient information to establish a point of departure for the assessment of the risk to humans resulting from all potential durations of exposure to 4-AP. Please comment on whether the studies are sufficiently sound, from a scientific perspective, to be used to derive a point of departure for estimating risk to humans from exposure to 4-AP.

b. Please comment on the following:

(1) Is there clear and convincing evidence that the conduct of any of the clinical studies was fundamentally unethical?

(2) Is there clear and convincing evidence that the conduct of any of the clinical studies was significantly deficient relative to the ethical standards prevailing at the time the research was conducted?

2:30 p.m. **Break**

AEATF and AHETF Research Programs

2:45 p.m. **Introduction – EPA Presentation**
William Jordan (EPA, OPP)

2:50 p.m. **Overview / Risks and Benefits of Handler Research – EPA Presentation**
Mr. John Carley (OPP, EPA)

3:30 p.m. **Public Comments**
3:45 p.m. **Board Discussion**

Risks and Benefits of Handler Research

1. Will the Task Forces' Governing Documents considered in conjunction with the additional study- and scenario-specific information specified above provide an adequate basis for assessing whether the risks of conducting a particular study are justified by the expected benefits of the proposed research? If not, what additional information should be provided for an IRB, EPA, and the HSRB?

5:00 p.m. **Addressing Potential Sources of Underestimation Bias/QA and QC Controls – EPA Presentation**
Mr. Jeff Dawson (OPP, EPA)
5:30 p.m. **Public Comments**
5:45 p.m. **Adjournment**

Friday, June 29, 2007

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

AEATF and AHETF Research Programs: Addressing Potential Sources of Underestimation Bias; QA and QC Controls (continued)

8:50 a.m. **Board Discussion**

Addressing Potential Sources of Underestimation Bias

1. Has EPA appropriately characterized the limitations on the scientific usefulness of a handler database that does not include data characterizing the efficiency of residue removal procedures? If not, what limitations have been overlooked?

2. Has EPA identified the relevant scientific and practical considerations affecting the choice to include biomonitoring, and has EPA appropriately characterized the limitations on the scientific usefulness of the resulting data if no biomonitoring is conducted? If not, what other considerations should bear on a decision to conduct biomonitoring in addition to WBD?

QA/QC Controls

1. Do the Task Forces' Standard Operating Procedures appear adequate to ensure that the data resulting from the proposed research will be of high quality? If not, what other Quality Assurance or Quality Control procedures need to be addressed?

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

10:15 a.m. **Design of Scenario-Level Sampling; Statistical Justification of Number of Clusters; and Monitoring Units and Within Worker Variability – EPA Presentation**

Mr. David Miller (OPP, EPA)

11:00 a.m. **Public Comments**

11:15 a.m. **Board Discussion**

Design of Scenario-Level Sampling

With regard to the AHETF and AEATF plans to conduct their proposed handler research using purposive diversity sampling strategies:

1. Has EPA identified the relevant scientific and practical considerations affecting the choice of a strategy for sample selection? If not, what other considerations should bear on the choice?

2. Does the HSRB agree with EPA that the Task Forces should provide scenario-specific information about the availability of data to identify significant variables (other than AaiH) potentially influencing exposure and about the feasibility of developing a sampling strategy to address those variables quantitatively? If not, what additional information is needed?

3. Has EPA appropriately characterized the limitations on the scientific usefulness of the resulting data attributable to the choice of the sampling strategy? If not, what has EPA overlooked?

Statistical Justification of Number of Clusters

1. What additional information, if any, would the HSRB need to assess the adequacy of the justification for the number of clusters and number of MUs in specific AHETF and AEATF study proposals?

Within-Worker Variability

1. Has EPA appropriately characterized the limitations on the scientific usefulness of a database that does not include repeated measures? If not, what limitations has EPA overlooked?

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

1:15 p.m. **Subject Recruitment and Enrollment Issues – EPA Presentation**

Mr. John Carley (OPP, EPA)

1:45 p.m. **Public Comments**

2:00 p.m. **Board Discussion**

1. Does the Board agree that the Governing Documents and associated SOPs of the AHETF and AEATF research programs include comprehensive and appropriate protections for human subjects of the research? If not, what has been overlooked?

2. In singling out the handling of language differences as an area requiring further refinement, has EPA overlooked other areas in need of revision? If so, what?

3:00 p.m. **Adjournment**

Steven Brimijoin, Ph.D. (HSRB Vice Chair) and Paul Lewis, Ph.D. (DFO, HSRB, OSA, EPA)

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