Minutes of the
United States Environmental Protection Agency (EPA)
Human Studies Review Board (HSRB)
April 13 – 14, 2011 Public Meeting
Docket Number: EPA-HQ-ORD-2011-0124
HSRB Web Site: http://www.epa.gov/osa/hsrb

Committee Members: (See EPA HSRB Members List—Attachment A)

Date and Time: Wednesday, April 13, 2011, 9:15 AM – 5:30 PM
Thursday, April 14, 2011, 10:00 AM – 1:10 PM
(See Federal Register Notice—Attachment B)

Location: Holiday Inn National Airport, 2650 Jefferson Davis Highway, Arlington, VA 22202

Purpose: The EPA HSRB provides advice, information, and recommendations on issues related to the scientific and ethical aspects of human subjects research.

Attendees: Chair: Sean Philpott, Ph.D., M.S. Bioethics
Vice Chair: Janice Chambers, Ph.D., D.A.B.T.

Board Members: George C.J. Fernandez, Ph.D.
Vanessa Northington Gamble, M.D., Ph.D.
Sidney Green, Jr., Ph.D., Fellow, ATS
Dallas E. Johnson, Ph.D.
Michael D. Lebowitz, Ph.D., FCCP
José E. Manautou, Ph.D.
Jerry A. Menikoff, M.D.
William J. Popendorf, Ph.D.
Virginia Ashby Sharpe, Ph.D.
Linda J. Young, Ph.D.

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

Convene Public Meeting and Review Administrative Procedures

Mr. Jim Downing (Designated Federal Officer [DFO], HSRB [or Board], Office of the Science Advisor [OSA], EPA [or Agency]) convened the meeting and welcomed Board members, EPA colleagues and members of the public. He thanked the Board members for their work in preparing for the meeting deliberations.

Mr. Downing noted that in his role as the DFO under the Federal Advisory Committee Act (FACA), he serves as liaison between the Board and EPA and is responsible for ensuring that all FACA requirements are met. The DFO must work with appropriate Agency officials to ensure

that all appropriate ethics regulations are satisfied regarding conflicts of interest; HSRB members have been briefed on federal conflict of interest laws and have completed a standard government financial disclosure report. In consultation with the deputy ethics officer for OSA and the Office of the General Counsel, Mr. Downing has reviewed the reports to ensure that all ethics requirements are met.

Mr. Downing informed members that there were four challenging topics on the agenda for the meeting, and agenda times are approximate. Copies of the meeting materials and public comments will be available at http://www.regulations.gov under docket number EPA-HQ-ORD-2011-0124. Following the presentations, time has been scheduled for questions of clarification to EPA staff and the principal investigator and sponsors of the studies discussed. This time is to be used for points of clarification rather than Board discussion. A public comment period will be maintained, and remarks must be limited to 5 minutes. During Board discussions, if members require clarification from the public, they may request such information through the Chair or DFO. All background materials for the meeting will be available in the public docket and most also are available on the HSRB Web site. Meeting minutes, including a description of the matters discussed and conclusions reached by the Board, will be prepared and must be certified by the meeting Chair within 90 days. The HSRB also will prepare a final report as a response to questions posed by the Agency that will include the Board's review and analysis of materials presented. EPA will announce the Board review and subsequent approval of the report in the Federal Register. Mr. Downing turned the meeting over to the HSRB Chair, Dr. Sean Philpott.

Introduction and Identification of Board Members

Dr. Philpott thanked the Agency and Board members for all of the planning and preparation for the meeting. He asked Board members to introduce themselves, and members completed their introductions. Dr. Philpott added that HSRB member Dr. José Manautou would be joining the meeting shortly, and invited Dr. Warren Lux (Director of the Program in Human Research Ethics, OSA, EPA) to offer welcoming remarks.

Welcoming Remarks

Dr. Lux welcomed all in attendance on behalf of EPA's Administrator and Science Advisor; they appreciate the Board's work and thank the members for their service. He thanked members for their patience during the previous week's numerous e-mails while the status of the meeting was uncertain due to the potential shutdown of the federal government.

Opening Remarks

Dr. Steven Bradbury (Director, Office of Pesticide Programs [OPP], EPA) also expressed his thanks that members had withstood the confusion during the past week. He noted that the Board's role in the business of the Agency and OPP is instrumental in ensuring that EPA is protecting human health and the environment by using the most ethical evaluations possible. He thanked the members for all of their hard work before, during and after the meeting. Two agenda items are critical: the work of the Agricultural Handler Exposure Task Force (AHETF) and the Antimicrobial Exposure Assessment Task Force II (AEATF II). Dr. Bradbury stated that EPA

believes that the studies to be reviewed reflect high-quality science and ethics; he expects the Board will agree, and having the information from these studies will improve the quality of risk assessments. Another agenda item concerns a journal article published in 2010, and this is the first time a study published after EPA's rule will be examined by the Board; EPA looks forward to learning from the experience. Ms. Kelly Sherman (OPP, EPA) will be discussing the proposed Human Studies Rule, on which the comment period recently closed. A few substantive comments were received, and EPA's goal is to meet its settlement agreement and sign the final rule by December 2011. Dr. Bradbury further thanked members for their efforts to examine methods to streamline the review and reporting processes so that appropriate studies can be used as promptly as possible in the risk assessment process. He thanked Drs. Philpott and Chambers for their role as Chair and Vice Chair of the Board. He also thanked Board members, Mr. Downing, and other members of OSA who prepared for the meeting. Finally, he thanked the public for their participation in the Board's efforts. He stated that the purpose of the FACA is to ensure that the Board's activities are open and transparent and that all interested parties have an opportunity to participate. He wished the Board a successful meeting.

OPP Follow-up on Previous HSRB Recommendations

Ms. Sherman stated that at the previous HSRB meeting in January 2011 the Board examined a completed closed-cab airblast study by AHETF, and EPA has determined that the data from the study represent the best available data for this use scenario. Following a review of the HSRB report to determine whether any adjustments, corrections or changes are needed on the exposure results, it will be used in future risk assessments of workers applying pesticides using closed-cab airblast equipment.

The Board also examined an AHETF protocol for mixing and loading of wettable powders. Based on comments from the Board and EPA, the AHETF has implemented recommended changes to the consent form, protocol and standard operating procedures (SOPs). The revised documents have received approval from Independent Investigational Review Board Inc. (IIRB). The AHETF is awaiting California Department of Pesticide Regulation (CDPR) approval. Once granted, recruiting will begin, and the AHETF hopes to monitor most of the subjects this summer, but monitoring may need to be completed in summer 2012.

Ms. Sherman informed the Board that the comment period for the proposed revisions to EPA's "Rule on Protections for Subjects in Human Research Involving Pesticides" closed on April 4, 2011, with only 10 comments received. This may reflect the fact that the changes being made were modest and the result of a settlement agreement with an environmental group. The most substantive comments are from some groups asking EPA to reconsider what is deemed an intentional exposure study. EPA is carefully reviewing the comments, and the Agency plans to have the final rule signed by the Administrator in December 2011.

Session 1: Completed AHETF Research on Workers Applying Pesticide Sprays Using Open-Cab Airblast Equipment

Background

Ms. Sherman (OPP, EPA) noted that this is a review of a completed study on application of pesticide sprays using open-cab airblast equipment. The AHETF is a group of 23 pesticide companies working together to develop new handler exposure data on 33 scenarios. The Board so far has reviewed protocols from five scenarios, and the reviews have been favorable. The completed field studies and monograph on closed-cab airblast received favorable HSRB review in January 2011. The open-cab scenario consisted of three field studies with a total of 13 subjects monitored. Dermal and inhalation exposure were monitored during pesticide application with open-cab airblast equipment to grapes in California (three subjects), grapes in New York (five subjects), and pecans in Oklahoma (five subjects). The data from these field studies have been combined with existing open-cab airblast applicator data of 15 subjects monitored in Georgia, Idaho and Florida. The protocols were reviewed by the HSRB in October 2008, with research conducted in July and August 2009, and data submitted to EPA in November 2010.

Ms. Sherman explained that the Board should consider whether the proposal was appropriately amended after review by EPA and the HSRB, executed faithfully, and conducted ethically and whether the results achieved the objectives.

EPA Science Assessment

Mr. Matthew Crowley (OPP, EPA) thanked his colleague Mr. Bayazid Sarkar (OPP, EPA) for his statistical analyses of the study data. The research objectives were to provide more robust and contemporary data and information for use in regulatory assessments of pesticides applied via open-cab airblast equipment by capturing the diversity and range of expected dermal and inhalation exposures. The data collected will be posted in a proprietary database. In terms of the data analysis, the primary objective is an accuracy objective: for dermal exposure normalized by the amount of active ingredient handled (AaiH), key statistics (geometric mean, arithmetic mean, 95th percentile) should be no more than three-fold lower or higher than their upper and lower 95 percent confidence limits. This benchmark is useful to guide the sample size. The secondary objective is, for dermal exposure and AaiH, to distinguish between a proportional and independent relationship with at least 80 percent statistical power.

The AHETF has shown in its governing document that in general, a 5 x 5 (n = 25) sampling configuration could satisfy objectives. In this scenario, there were existing and acceptable open-cab airblast applicator data (n = 15). In this case, the goal was 30 monitored applicators. Diversity selection was employed, with recruitment randomized to minimize selection bias. As a result of this strategy, EPA recognizes that there are limitations in terms of statistical inferences that can be made.

Because this study design was so similar to the closed-cab study, comments were almost identical, and EPA believed that the AHETF had addressed the HSRB's comments. The existing study (AHE07) was conducted on five males spraying peaches in Georgia, six males spraying

apples and pears in Idaho, and four males spraying oranges in Florida. The new studies consisted of three males spraying grapes in California (AHE62), five males spraying grapes in New York (AHE63), and five males spraying pecans in Oklahoma (AHE64). In the California grape study, five subjects had been planned, but only three could be recruited. To apply the pesticides, 28 different pieces of equipment were used. Some had shade canopies, as noted in the CDPR's initial review of the protocol. The average number of tank loads was four, the average volume sprayed was 1,809 gallons, the average treated area was 16 acres, and the average time was 5.8 hours. In the existing studies, the subjects handled the high end of the targeted range of AaiH, so subjects were placed into specific AaiH strata in the new studies to meet both primary objectives. In AHE62, two of the strata were unfilled because there were only three subjects, and in AHE64, one stratum was not filled because a subject went outside the predetermined strata. Exposure monitoring methods included hand wash, face and neck wipes, inner and outer patches worn because a chemical resistant hat also was worn, a whole body dosimeter (WBD), air pump, and Occupational Safety and Health Administration Versatile Sampler (OVS) tubes. Socks were used in the existing study but not in the new studies. Analytical limits show that measurements below the detection limits mainly were avoided.

Deviations from the protocol included fewer than three tank loads sprayed, spraying time of less than 4 hours, unverified field fortification concentrations, failure to meet AaiH strata targets, and modifications to analytical methods. In EPA's opinion, none of these deviations undermined or compromised the exposure results. The AHETF's Quality Assurance Unit ensures that studies follow EPA Good Laboratory Practice (GLP) Standards (40 Code of Federal Regulations (CFR) part 160), including that the task force personnel are trained, site and equipment inspections are conducted, protocols and amendments are reviewed, reports are audited, and individual study reports include signed Quality Assurance Statements. Both negative controls (blanks) and positive controls (spikes) were included in the study. It was noted that some residues were detected in AHE07 blanks in the laboratory, and in the field, the only residue greater than the limit of quantitation (LOQ) were in the OVS tube. In the laboratory, all spikes were in acceptable range; some unusual results were noted for the field spike samples. Some differences also were found between days, and instances of this type occurring in the future could perhaps be discussed in the report. Exposure monitoring results represent workers wearing long-sleeved shirts, pants, chemical-resistant gloves, shoes/socks, and no respirator, with or without chemical-resistant hats. All measurements are adjusted by average recovery of corresponding field fortification matrix and level, and a few left-censored measurements were noted (mostly OVS back sections). Based on recommendations from previous HSRB meetings, if the measured contribution from hands and face/neck represents between 20 and 60 percent of the total, measurements are to be adjusted upward by two, or a validation study supporting the method's efficiency must be provided. The HSRB's greatest concern about combining the data would have been if the pre-rule studies were a magnitude higher or lower than the new data set, but they fall in the same general range.

Some of the open-cab vehicles had shade canopies. In the AHE64 study, only one of the subjects reported having a canopy, but there were in actuality two additional workers who had canopies; still, EPA determined that their presence did not have a significant effect on exposure. Estimates of exposures normalized by AaiH ("unit exposures") were summarized in task force submissions using three methods: empirical estimates; simple random sample (lognormal,

independent); and a mixed model (lognormal, nested). Considering data structure, the mixed-model is most appropriate. Magnitude of exposure was greater for subjects without chemical resistant hats. Plots should be examined for the degree to which like symbols are grouped together, the intraclass cluster correlation.

In the inhalation exposure data, one worker (A5) in AHE64, if excluded, decreases the arithmetic mean and 95th percentile substantially. In correspondence with the task force and in the report, no mismeasure can be attributed to worker A5, so the reasons for the lower inhalation exposure in this individual are unclear. A more conservative approach is taken by using the entire data set. Data show that the primary objective analytical benchmark was satisfactorily met, with no additional monitoring necessary. For the secondary objective examining the relationship of the AaiH and exposure, it is noted that for routine EPA handler assessments, exposure is predicted from AaiH, which assumes that the two are proportional. The AHETF research design is intended to result in 80 percent statistical power to distinguish independence from proportionality. Data were found to be consistent with proportional relationship if 95 percent confidence intervals (CI) of the regression slope include 1, whereas 80 percent power is achieved if the width of the 95 percent CI is 1.4 or less. The secondary benchmark was not met; post-hoc analysis shows less-than-expected power. The proportionality with AaiH is consistent with dermal exposure data, however, even with less-than-expected power, and proportionality and independence with AaiH are consistent with inhalation exposure data.

In conclusion, the research design is acceptable, despite the lack of random sampling; statistical inference requires assumption that the sample is representative of the range of exposure for all U.S. open-cab airblast application-days; monitoring methods and results were consistent with EPA guidelines and previous studies; acceptable analysis of research objectives was conducted, and no additional monitoring is necessary for this scenario; and the data are recommended for use in regulatory assessments with AaiH normalization as a default condition, but are not applicable for high volatility chemicals.

Board Questions of Clarification—Science

Dr. William Popendorf inquired whether a test was conducted to determine whether the studies and crops were the same in terms of this completed study. Does an intraclass correlation of zero mean there are crop differences that affect exposure? Mr. Crowley responded that a test was not conducted. Mr. Sarkar added that each cluster had a different crop, but no test had been conducted.

Dr. Dallas Johnson noted that, regarding slide 27 of EPA's presentation, which deals with log normal probability plots, the intraclass correlation might relate if the same amount of active ingredient (ai) was applied at each case, but because the AaiH is spread out, no statements can be made about what points are clustered together. Dr. Philpott added that this could be an important point for discussion.

Dr. Chambers asked whether analytical methods for the existing study and new studies were the same. Mr. Crowley replied that in all cases except for the OVS tubes and WBD there

were slight differences in the methods, but remainder were the same. In terms of more specifics, he would defer to the AHETF.

Dr. George Fernandez stated he had some difficulty understanding in slide number 9 of EPA's presentation the phrase "no more than three-fold lower or higher than upper than their upper and lower 95 percent confidence limits." Mr. Crowley suggested that members see slide 31, which provides a better explanation. In each case, 95 percent confidence limits are derived. To compare these statistics to the lower confidence limit, the statistic would be the numerator in that ratio, and the denominator would be the upper confidence limit. EPA is looking for the larger of those to be less than three. Dr. Fernandez noted that in slide number 28, the range is very large for the 95th percentile. Mr. Crowley responded that as long as the 16,340 divided by 6,148 is less than three, that is acceptable. Dr. Fernandez asked whether there were acceptable biological or toxicological limits. Mr. Crowley stated that it was not related to toxicology but rooted in uncertainty in the assessments. Dr. Philpott asked, for the products used, whether these numbers were within the established range for the handlers. Mr. William Jordan (OPP, EPA) added that, from a science policy point of view, the K-factor addresses setting a standard for the degree of accuracy in the assessments that are derived from the dataset and various statistical intervals. If there were more subjects monitored, the ranges would be smaller. It is a trade-off between the cost of generating additional data and the value of having smaller ranges. The ranges of these datasets will be large, and there are subsequent science policy questions that EPA addresses in risk assessments: What value does the Agency get from the dataset? What values from the dataset should be used?

Dr. Sidney Green commented that it was stated that protocol deviations did not undermine the study results and asked who makes that determination. Mr. Crowley answered that one person is assigned to conduct the review and, in consultation with other experienced scientists in this area, makes the determination. Dr. Green asked whether that was EPA's policy. Mr. Jordan stated that Mr. Crowley described the standard review process that EPA uses. A staff-level reviewer performs the initial examination of the dataset and study report and as part of that review, notes any places in the report that a departure from protocol or other irregularity is seen. Internally, there is a group of people that has been conducting these sorts of reviews for many years, including Mr. Jeffrey Dawson (OPP, EPA) and Mr. Jeff Evans (OPP, EPA). They collectively consult on the initial reviews and decide whether they agree with the conclusions of the initial review. That is a very standardized process. If an issue does not have consensus, more people will be consulted, up to the Scientific Advisory Panel (SAP) if the issue is difficult or significant enough. Each reviewer must explain his or her rationale for the positions stated. Mr. Dawson added that the task force has a quality assurance unit, so there is a process under GLPs in which they would make their determinations that would come to EPA in a documentation report.

Dr. Johnson commented that it was important to keep the scale the same when more than one graph was presented on the same slide, such as on slide 27 of EPA's presentation. Dr. Michael Lebowitz stated that one method by which to accomplish that is to show the regression.

Dr. Linda Young questioned, on slide 34, whether the data that give rise to the slide are in table S24 of the members' handouts, and if not, where they could be found. Mr. Sarkar responded that the data for that table are in Appendix G, page 33.

Dr. Philpott invited representatives of the AHETF to the table to answer questions. Dr. Victor Cañez, consultant to the AHETF, and Mr. Richard Collier, chair of the administrative committee of the AHETF, joined the members.

Dr. Popendorf noted that the work time varied and asked what the "gold standard" was for monitoring time. Dr. Cañez stated that generally the monitoring time is from when the pump is turned on to when it is turned off. There may have been some discrepancies in the pump, such as a need to change batteries.

EPA Ethics Assessment

Ms. Sherman noted that in terms of recruiting, the three-phase process outlined in the protocols and SOPs generally was followed. The AHETF generated an initial grower list from published lists and databases and narrowed the list using qualifying questions. Qualified and interested growers were contacted by the study director to identify those who could participate within a timeframe and schedule that would allow an efficient study. Several protocol amendments were made: the inclusion criteria were amended to allow participation by individuals who normally wear two layers of clothing (subjects could wear a coverall over the WBD); the recruitment process was modified to allow for use of recruitment letters sent directly to growers; and the permissible recruitment area was expanded.

The consent process outlined in the protocols and SOPs was closely followed in all three studies with no reported or unreported deviations. All of the subjects were males. Only three subjects were monitored in California, whereas the other two studies each monitored five. All but one subject in California, who preferred Spanish, preferred the consent process be conducted in English. No subjects made use of a witness. All were farm owners or operators except for one farm employee in California. Ages across the studies ranged from 28 to 79, and all requested their results.

Exposure monitoring was conducted without incident, with no adverse events, incidents of concern, or withdrawals from the research. The greatest risk in the study was heat-related illness. The temperatures did not rise to the heat index cutoffs for the study, and procedures in the SOPs were followed in terms of announcing changes in temperature and monitoring the workers.

The initial protocol was reviewed by IIRB, with seven amendments and seven deviations reviewed by IIRB through expedited procedures. Additional amendments included the lowering of the heat index stopping rule to 105°, and AHE62 added a new malathion product. Only a few minor deviations were noted, and none were of ethical significance. Most involved missing the target of three tankloads or 4 hours monitoring time.

The AHETF successfully responded to both EPA and HSRB comments made during the protocol review. Regarding documentation, IIRB correspondence volumes are complete and

well-indexed, and requirements of 40 CFR §26.1303 are satisfied. EPA's substantive acceptance standards include 40 CFR §26.1703, which prohibits reliance on data involving intentional exposure of pregnant or nursing women or of children; 40 CFR §26.1705, which prohibits reliance on data unless EPA has adequate information to determine substantial compliance with subparts A through L for 40 CFR part 26; and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) §12(a)(2)(P), which makes it unlawful to use a pesticide in human tests without fully informed, fully voluntary consent.

Ms. Sherman found that all substantive acceptance standards were met: all subjects were at least 18; pregnant or nursing women were excluded; no significant deficiencies were noted in the ethical conduct of the research; the protocol was faithfully executed; deviations did not compromise the safety or consent of subjects; and subjects were fully informed, and their consent was fully voluntary, without coercion or undue influence.

In conclusion, available information indicates that the AHETF open-cab airblast studies (AHE62, 63, 64) were conducted in substantial compliance with subparts K and L of 40 CFR part 26.

Board Questions of Clarification—Ethics

Dr. Jerry Menikoff inquired why the amendment to lower the heat index that was made to two of the studies was not made to the third study. Ms. Sherman responded that she was unsure and had not followed-up with the task force. But, the heat index limit was amended in the SOP after this study, which will deal with the issue in the future.

Dr. Popendorf asked about the list in California being winnowed from 4,000 to four potential participants and whether all 4,000 names had been called. Ms. Sherman replied that she thought they had called all 4,000. Dr. Cañez confirmed that all were called, and many do not answer because of caller identification. Dr. Cañez added that in California only a small percentage of the users employed open cabs, and few wore the right type of personal protective equipment for the study, so the AHETF was led to a very small number of subjects. Dr. Philpott noted that Dr. Manautou had joined the discussion and that Mr. Robert Roogow of IIRB was in attendance.

Dr. Philpott noticed a clarification on the protocol of the AHETF's raw data retention policy. He questioned whether this was a change in the policy or just a modification of the protocol to clarify what already was being done. It states, "In accordance with GLP regulations 40 CFR part 160.195 and SOP 6.8, raw data will be retained in the archives as long as the task force for the other registrar holds a research or a marketing permit to which the study is pertinent." Dr. Collier responded that it was a way to document the fact that that is a requirement of GLP; the AHETF already was doing this.

Public Comments

Dr. Philpott offered Drs. Cañez and Collier a chance to make a public comment of up to 5 minutes, but they declined. Dr. Cañez noted that Dr. Larry Holden, the AHETF's statistician, was

in attendance and available to answer questions. Dr. Philpott then offered Mr. Roogow of IIRB an opportunity to give public comment. However, Mr. Roogow did not provide any further comments.

Dr. Philpott invited additional public comment on the AHETF open-cab airblast study; no public comments were presented. He noted, however, that one written comment had been received in response to the Federal Register notice of the meeting. It is somewhat extensive, so he did not read it into the record but noted that it was available in the public docket. It is from Ms. Carol Dansereau, Executive Director of the Farm Worker Pesticide Project in Seattle, Washington, and Executive Director of the Washington Toxics Coalition. There is some relevant information in her statements that is pertinent to the Agency and the Board, particularly with respect to questions of engagement of additional stakeholders, whose discussions the Board will play closer attention to, and Dr. Philpott will examine whether there is adequate community representation and input at future HSRB meetings. He encouraged members to read the comment during the break. Dr. Vanessa Northington Gamble mentioned that she had studied the comment and noted that it raises questions about public engagement and who is considered an expert. She went to the announcement of the meeting, and it says the meeting would be of particular interest to people who assess or conduct human studies; people who might be affected or participants of studies are not mentioned nor are experts on community engagement. The comment raises serious questions about the meeting announcements but also the composition of this Board.

Charge Questions

Ms. Sherman read into the record the three charge questions:

1. Was the research reported in the AHETF completed monograph report and associated field study reports faithful to the design and objectives of the protocol, SOPs and governing documents?
2. Has the Agency adequately characterized, from a scientific perspective, the limitations on these data that should be considered when using the data in estimating exposure of those who apply conventional pesticides with open-cab airblast equipment?
3. Does available information support a determination that the studies were conducted in substantial compliance with subparts K and L of 40 CFR part 26?

Board Science Review

Dr. Philpott requested that the Board members focus their discussion on the two scientific charge questions.

Dr. Popendorf thought that overall, the study addressed many of the concerns expressed by the HSRB in its review, and the inclusion of local experts was useful and appropriate. The better definition of the recruitment process was useful, as was inclusion of the scripted records. Although there was no formal test of the difference between crops, the visual evidence is very strong, and he would support grouping the crops and the clusters as proposed by the Agency. It also was very useful to have the broader interests examine the differences between open and

closed cab. The use of the head patches was innovative. The head accounted for about 18 percent of exposure, hands 27 percent, and the rest of body 56 percent. In terms of the hat, good data are generated if the hat is used, but if it is always used, it will affect the estimate of "no hat." The brim of the hat always had some effect. Dr. Popendorf is comfortable with an affirmative answer on the first charge question.

Dr. Chambers agreed that the study was faithful. She examined the methodology, quality assurance and quality control. Recoveries were in a good range, and the AHETF followed the protocol with the same sort of sampling as had been conducted in the past, with the same sorts of dosimeters. Dr. Young also agreed that that study was satisfactory. Dr. Philpott stated that on the teleconference meeting regarding the previous Board report, there was some question about the primary objective as described in the study. He asked if Dr. Young and Dr. Johnson wanted to speak to that point for this study.

Dr. Philpott noted that the consensus of the Board is that research reported in the AHETF completed monograph report and associated field study reports was faithful to the design and objectives of the protocol, SOPs and governing documents.

On the question of adequate characterization of the limitations of the data that should be considered, Dr. Popendorf noted that the brim of the hat probably reduced exposure to the rest of the face. A small change would be not including the inner patch when examining the "no hat" exposure, because the outer patch on the hat measures what would have been the cause of the exposure. At the same time, the face probably was protected by the brim. Because the subjects always wore a hat, there is no way to know what that protection was, but the actual face exposure without a hat was not measured. On the air samples, the LOQ greater than two was used for the backup air sample, which should be zero. Material should not have reached the backup. The Kinkelder airblast sprayer should be listed in the limitations, as it is known to be a high drift machine. Several comments were made about participant AHE64 A5, but several observations were missed. One of the notations was that the nozzle pressure for this monitoring unit (MU) was twice the recommended maximum pressure. Additionally, this MU changed from spraying in both directions to spraying in only one direction for the last one-third of his application time. This is the only MU for whom this notation was made. Information in the record implies that the MU made a conscious effort to apply in an upwind direction to minimize wind exposures.

Dr. Young returned to the measures, particularly the limitations that are present in some of the measures. There are ranges of AaiH and therefore exposures over wide space, so what does it mean to take the arithmetic mean? The arithmetic mean is taken by exposure divided by ai, which makes sense if exposure is proportional to ai. The test of that assumption seems to be critical. The geometric mean appears to be based on the assumption that the log of exposure is equal to a constant times log ai. If the arithmetic mean makes sense, the geometric mean does not and vice versa. In one of the models, the log of exposure divided by ai is equal to some constant; this would be valid if the ratio of exposure to AaiH is equal to the exponentiation of some constant. Three measures are used, each of which makes sense if an assumption is true. Checking assumptions is vitally important. Dr. Chambers inquired whether checking the assumptions would require experimentation. Dr. Young responded that this goes to analysis of the data and must be performed very carefully.

Dr. Philpott summarized that the general consensus is that the Agency has satisfactorily characterized limitations, but there are additional limitations that need to be considered with respect to using the data and estimating the exposure. These include consideration of whether the inner patch is measuring penetrance; it is unclear whether this will affect the results, but it should be considered in analysis as well as the protection of the face by the brim. There were concerns about the use of LOQ over two for the backup sample; the backup sample should be zero if it was a proper sample, and giving it a different value will bias the results. Some consideration must be paid to the 28 different types of equipment that were used, particularly the high drift machine. With respect to the one participant who had a low exposure, there are some additional factors that may explain why, such as the high nozzle pressure he used and change in the application approach from two-sided to one-sided. He may have changed application because he was on a slope or because of the wind. This should not be taken as a recommendation as to whether to exclude that participant from the analysis but may indicate why he has reduced exposure. Dr. Young raised some concerns about statistical analyses and that each of the three measures all relied on assumptions that must be tested in the analysis of the data.

Mr. Sarkar noted that to calculate arithmetic mean, geometric mean, and 95th percentile, first the log of exposure over AaiH on the intercept is calculated. From there, EPA calculates the arithmetic value of intercept, and then the arithmetic mean is calculated. Information on the formula is on page 18 and Table 9 of EPA's report. The geometric mean is calculated exponential to the intercept. Dr. Young stated that in performing calculations in this manner, EPA was assuming the model was correct. She said that Mr. Sarkar had to address carefully each of the assumptions associated with that model. Dr. Philpott noted that the recommendation is that the assumptions being used in the fitted model must be checked.

Dr. Popendorf clarified that the effect of the patch is small, on the order of 1 percent.

Board Ethics Review

Dr. Menikoff concluded that the available information supports a determination that the studies were conducted in substantial compliance with subparts K and L of 40 CFR part 26. This is a type of study with which the HSRB is becoming more familiar and gradually has been refined based on HSRB recommendations over a period of time. He agrees with Ms. Sherman's determination. Risks generally have been minimized; the studies are well-designed to take advantage of activities that would normally be taking place within the subjects' daily employment. There is a positive risk/benefit ratio. Informed consent was obtained appropriately, and specifically, noting that 12 of the 13 subjects are owner/operators, there likely is less concern about the subjects being vulnerable. Dr. Virginia Ashby Sharpe concurred with Dr. Menikoff's analysis. Dr. Philpott concluded that the general consensus answer to the question is that the available information supports a determination that the studies were conducted in substantial compliance with subparts K and L of 40 CFR part 26.

Session 2: A Published Report (Gulson et al. 2010) of an Intentional Exposure Human Study Measuring Dermal Absorption of Zinc Oxides Contained in Sunscreens

Background

Dr. Jessica Ryman-Rasmussen (OPP, EPA) informed the Board that the Agency has pending registrations for articles treated with nanoparticle-based pesticides (e.g., textiles, plastics, wood) and is conducting quantitative, screening-level risk assessments for these products, including dermal assessments that require quantitative estimates of dermal penetration of nanoparticles. Generic Dermal Assessment Questions include: (1) What is the rate and form of the compound released (transfer efficiency) from the treated article? (Application Rate × Density × Surface Area Exposed × Transfer Efficiency) (2) What is the dose? ([Exposure (milligrams per day (mg/day)) × Dermal Absorption Factor]/Body Weight (kilograms (kg)).

EPA Science Assessment

Few studies in the literature allow a quantitative estimate of dermal absorption from nanoparticle exposure, but the Agency recently identified a study by Gulson et al. (2010) that quantitatively estimates dermal penetration of zinc (Zn) from zinc oxide (ZnO) nanoparticles in a sunscreen formulation in human volunteers. This study was conducted at an aquatic center and a Sydney, Australia beach, and its objective is to determine whether Zn from nanoparticles in sunscreen can be absorbed through healthy skin under normal conditions of sunscreen use. The test substance used was ZnO enriched to 99 percent with ^{68}ZnO (a nonradioactive isotope) in two sizes, 110 ± 46 nanometers (nm) (25–284 nm) and 19 ± 8 nm (3–60 nm), in a sunscreen formulation containing isopropyl myristate, a penetration enhancer, and ethylenediaminetetraacetic acid (EDTA), a Zn chelator. ^{68}Zn can be measured by multicollector inductively coupled plasma mass spectrometry (MC-ICP-MS).

The study applied ^{68}ZnO in sunscreen formulation two times per day for 5 days in the amount of 3.7 to 4.6 mg/square centimeter (cm^2) to a 500 cm^2 area of the back in a cut out area of an ultraviolet (UV)-protective upper body garment. After the sunscreen was applied to the subjects, they were told to lie down in the sun for 30 minutes and allow the sunscreen to absorb into the skin. After the 30-minute time period, the subjects were free to participate in beach-like activities. A diary of these activities was kept, estimating the amount of UV exposure that occurred. The sunscreen was removed at the end of the day with alcohol/lanolin wipes. The amount removed was not quantified. Blood and urine samples were taken from all subjects before exposure, at Day 5, and after exposure. For some subjects (one per gender for both 110 ± 46 nm and 19 ± 8 nm), blood also was collected on Days 2–4 of exposure, and for some, 19 ± 8 nm (three men, one woman) urine samples were taken out to 25 to 40 days post-exposure. For urine collection, there is the potential for contamination via hands, particularly in women.

^{68}Zn levels were measured in the urine and blood by measuring ^{68}Zn/ ^{64}Zn via MC-ICP-MS at different times (^{68}Zn% is greater than zero only if ^{68}Zn from sunscreen was absorbed). ^{68}Zn could be in ionic ($^{68}Zn^{+2}$) and/or nanoparticle (^{68}ZnO) form. Two methods were used (as a result of uncertainties in estimating natural Zn reservoir in individuals). The percentage of

applied ^{68}Zn absorbed into blood was calculated by the change in (Δ) ^{68}Zn% adjusted for fat-free body mass (estimated via body mass index) and measured blood Zn and $\Delta^{68}Zn$% adjusted for total blood Zn concentration (based on blood volume).

Authors stated that $^{68}Zn/^{64}Zn$ increases in blood for all subjects with and after exposure, but no statistical analysis was provided. A Wilcoxan test of $\Delta^{68}Zn$ percentage comparing exposure and post-exposure found a highly significant difference (p is less than 0.0001). Analyses of variance on $\Delta^{68}Zn$ percentage adjusted for fat-free body mass and/or blood volume show the effect of gender and particle size (19 ± 8 nm females is greater than all others) at p = 0.053 and p = 0.051. These data indicate that blood levels continue to increase after exposure, which indicates that there is potential for absorption of skin-bound residues of sunscreen. There was a 2-day lag in the ability to detect ^{68}Zn above baseline levels. The researchers also measured $\Delta^{68}Zn$ in urine; EPA evaluated these data and considered the results equivocal because there was evidence that the samples had been contaminated, but results seemed to support blood results. The percentage of the applied dose of ^{68}Zn absorbed from ^{68}ZnO sunscreens was estimated at about 0.001 percent.

Study limitations included: the detection method does not discriminate between particles and ions; absorption could be underestimated because it is unknown whether ^{68}Zn from ^{68}ZnO is partitioned into other organs/tissues (besides blood), it is unknown how much rubbed off, and the sunscreen formulation contains Zn chelator EDTA; absorption could be overestimated because the sunscreen formulation contains a penetration enhancer, isopropyl myristate; there is uncertainty in estimating the magnitude of the natural Zn reservoir in each individual. In conclusion, small amounts of Zn in ionic or oxide form (about 0.001 percent) from ZnO nanoparticles in sunscreen formulations can penetrate healthy skin in human volunteers.

Board Questions of Clarification—Science

Dr. Manautou inquired about the length of time between the first and second dose. Dr. Ryman-Rasmussen answered that this was not stated in the study. Dr. Manautou asked whether the authors provided any justification for the selection of the four individuals from which the complete urine samples were analyzed. Dr. Ryman-Rasmussen responded that they did not. Dr. Manautou questioned whether there was any indication of how the information on the ai, which was 51 percent enriched in the pilot study, was used to influence the final study design that used a 99 percent Zn isotope. Dr. Ryman-Rasmussen responded that it was not mentioned in the publication, but EPA had some correspondence with the authors, and the pilot studies were conducted to determine how much the isotope would need to be enriched to get reliable detection. The 51 percent was not efficient. Dr. Manautou asked whether there was justification of why frequency and time of garment changes and specific activities were not recorded. Dr. Ryman-Rasmussen responded that there was no information about these issues in the published study.

Dr. Popendorf noted that the application site was 500 cm^2, and Dr. Ryman-Rasmussen confirmed that this was not in the study but information that was received from the authors.

Dr. Chambers asked whether any other insights were received from the authors. Dr. Ryman-Rasmussen inquired about the surface area of application and sought further information on calculations that was not provided.

Dr. Green asked whether environmental conditions were monitored. Dr. Ryman-Rasmussen did not ask the authors for this type of information. Dr. Green noted that the hydration status of the skin based on temperature and humidity can affect absorption.

Dr. Fernandez asked whether the Agency analyzed the data, and Dr. Ryman-Rasmussen replied that she was told that sample calculations were not available, so EPA did not conduct data analysis. Dr. Fernandez asked about female subject 7, who had a high amount of penetration. This extreme data point could have contributed to the overall finding affecting the female absorption of nanoparticles. Dr. Ryman-Rasmussen noted that the authors addressed this in the paper; the female with the adverse skin reaction might have biased that entire treatment group, but the data were normalized (log normal), so the authors were confident that the results were not biased.

Dr. Northington Gamble noted that skin types from one to four were mentioned in the paper, and it is unclear what that means. Dr. Ryman-Rasmussen responded that skin type is a standard classification for skin based on pigmentation. Dr. Northington Gamble asked how that is determined in terms of gradations. Dr. Ryman-Rasmussen replied that the authors did not say how they determined skin type, but skin typing is fairly common in medical and cosmetic industries. Dr. Johnson asked what would constitute a type 4. Dr. Ryman-Rasmussen noted a data table that mentions the countries of origin for the subjects in the study; South American females were classified as skin type 4, and German and Australian females were classified as skin type 1.

Dr. Johnson added that the authors did not address whether the difference in the amount of Zn present is significant. Dr. Ryman-Rasmussen stated that there is much debate about whether nanoparticles can penetrate intact healthy skin. This is the first study that provided evidence that nanoparticles or ions released from nanoparticles penetrate intact skin of human volunteers. Although the amounts are small, it still may be important because it is unknown what exposure to nanoparticles is hazardous. The method, however, does not discriminate between Zn ions or nanoparticles. Dr. Manautou added that the paper does not address whether it is assessing Zn ions or Zn nanoparticles in the body. Dr. Ryman-Rasmussen agreed that this could not be determined, but if risks are assessed for both particle and ion based on this estimate, then that still is helpful to the Agency because it still allows a quantitative estimate of dermal penetration. Dr. Manautou noted the difficulty in understanding the utility of the paper because it may have nothing to do with nanoparticles. Dr. Ryman-Rasmussen responded that the conservative approach is to assess for both nanoparticles and ions using 0.001 percent.

Dr. Philpott stated that not all skin is the same and asked about vascularization and whether it could affect Zn detection. Dr. Ryman-Rasmussen answered that skin is relatively avascular compared to other organs. When EPA discusses the dermal absorption, it is assuming that the 0.001 percent in the blood is systemically available and is used to calculate an internal dose from a topical application.

Dr. Fernandez mentioned that researchers did not conduct comparisons between the skin types or address age. Dr. Ryman-Rasmussen agreed that they did not but could not say with any certainty whether that would have resulted in different conclusions. The authors have a good sampling of age ranges in the study. Skin thickness and hydration status will have the most significant influence on absorption. Females tend to have thinner skin than males, and for the smaller particles, that may have been a potential explanation for why there was greater absorption.

Dr. Popendorf noted a difference in the natural metabolism of isotopes by their molecular weight. Dr. Ryman-Rasmussen commented that she had not conducted any investigations on how the particular isotope of Zn may affect the biodistribution.

EPA Ethics Assessment

Ms. Laura Parsons (OPP, EPA) presented EPA's ethics assessment. Research was conducted in Australia in 2009, so it was subject to the Australian National Statement on Ethical Conduct in Human Research, which covers all research with human subjects in Australia and is similar to the U.S. Common Rule, with governing principles of respect, research merit and integrity, justice and beneficence. This is the first time that EPA has asked the HSRB to review a study that EPA located in the public literature that was conducted after the EPA 2006 Human Studies Rule. So in this case, 40 CFR §26.1303 and FIFRA §12(a)(2)(P) do not apply. The research provides information on dermal absorption of Zn from sunscreen applied to healthy human skin under conditions of normal use.

Ten men and 10 women, ages 19 to 66, participated in the study. Recruiting for this study was done through personal contacts of the researchers after other recruiting methods failed. Dr. Brian Gulson, principal author of the study, noted that researchers attempted to recruit via e-mail and a presentation at a local beach club. Several family connections existed among the subjects, but it was unclear whether there was connection between the researchers and subjects. The Australian National Statement does not preclude this kind of recruiting. Dr. Gulson also stated that none of the females in the study were pregnant or nursing; it is unclear if they were tested.

Researchers identified the main risks as from phlebotomy and adverse reactions to sunscreens. A trained professional drew the blood samples, and subjects were questioned regarding their sensitivity to personal care products to minimize this risk. One subject had a skin reaction, but the nature of the reaction was unclear. The benefits and compensation were not discussed in the article. Societal benefits were thought to outweigh the minimal risk. The Macquarie University Human Research Ethics Committee oversaw and approved the research. Approval was made in May 2008 and covered the period through May 2009; research was conducted in March 2009.

Written consent is not required by the Australian National Statement but was obtained before the commencement of this trial. One participant withdrew before the trial began, two withdrew during the 5-day application period, and one subject was withdrawn for an adverse reaction. Subjects were informed of the risk and were free to withdraw. Dr. Gulson did not provide an informed consent form to EPA.

The applicable standards of conduct are the Declaration of Helsinki and the Australian National Statement of Ethical Conduct in Human Research. In the publication, the authors "certify that the research met with full compliance with all government policies and the Helsinki Declaration." The Letter of Final Approval from the Macquarie University Ethics Review Committee is the "usual document that researchers use to show that the research has been through the appropriate ethics review process…and meets the requirements of the National Statement." Standards of acceptability for EPA's reliance on these data are 40 CFR §26.1703, Prohibition of reliance on research involving intentional exposure of human subjects who are pregnant women (and therefore their fetuses), nursing women, or children, and 40 CFR §26.1705, Prohibition of reliance on unethical human research with non-pregnant, non-nursing adults conducted after April 7, 2006. No pregnant or nursing women were included in the study, and the Australian National Statement, complied with by the researchers, is as protective as U.S. Common Rule. In conclusion, if the study is deemed scientifically valid and relevant, there are no barriers in FIFRA or 40 CFR §26.1703 or §26.1705 to EPA's reliance on the Gulson et al. study in actions taken under FIFRA or §408 of the Federal Food, Drug, and Cosmetic Act.

Board Questions of Clarification—Ethics

Dr. Sharpe remarked that the report stated that blood and urine samples were taken 8 days before exposure, and informed consent was received 1 week before exposure. Ms. Parsons assumed that the 1 week was prior to the blood and urine samples being taken, but this is not stated explicitly in the paper.

Dr. Northington Gamble noted that in the 2007 National Standards of Australia it is clear, in a discussion of power dynamics, that coercion in a relationship between a researcher and the participants is prohibited. In one of the letters provided from Dr. Margaret Stuart, Director of Research Ethics at Macquarie University, she asked about this issue, because the term "personal contacts" is unclear. Ms. Parsons noted that the final letter providing approval did not follow up on this point, and she did not specifically ask that question.

Dr. Sharpe inquired about the rationale for the conclusion that the study is acceptable for consideration by EPA. Ms. Parsons responded that she had documentation that the National Statement was followed and also considered the parameters of the national statement itself.

Public Comments

Dr. Philpott called for public comments on the published Gulson et al. study; no public comments were presented.

Charge Questions

Ms. Parsons read the charge questions into the record:

1.Is the Gulson et al. study scientifically sound, providing reliable data?

2. If so, is the Gulson et al. study relevant to an assessment of the absorption of zinc oxide through the skin?
3. Is there adequate information to determine that the Gulson et al. study was conducted in substantial compliance with procedures at least as protective as those in subparts A–L of EPA's regulation at 40 CFR part 26?

Board Science Review

Dr. Manautou noted that if data reliability is being questioned in terms of skin penetration by ionic Zn, the answer to the first charge question is yes. If data on the penetration of nanoparticles are being questioned, the answer is no. Regarding the second charge question, if dealing with absorption of ZnO or soluble Zn, the answer is yes with some caveats on the experimental design.

Dr. Chambers stated that her interpretation was that only Zn was being addressed, not nanoparticles. There was no untreated control, which is a flaw. Additionally, the person who applied the Zn was wearing a glove but also had an increase in Zn over time, which leaves the data a bit suspect. A controlled study would provide needed answers, but a beach scenario is not controlled. The sunscreen contained isopropyl myristate, which would not be used in a controlled study. The skin was washed with alcohol and lanolin, which also could affect the absorption of the compound. It is unknown whether dissolved Zn or Zn nanoparticles were absorbed. There is an overlap in the two size categories, so distinguishing between the two groups will be difficult. For what was done, it is scientifically sound, but in terms of how relevant it is to determining absorption of ZnO through the skin, many limitations mentioned above must be considered.

Dr. Fernandez commented that Dr. Ryman-Rasmussen had mentioned controversy about whether nanoparticles were absorbed by intact skin and that this study could be considered a pilot study because of the small sample size, issues about how the samples were selected, and inclusion of an extreme data point. He questioned the reliability of the data and stated that further studies are necessary to confirm the data.

Dr. Manautou stated that although he did see the strengths in the data on dermal penetration of soluble Zn, the third bullet on slide 4 of EPA's presentation mentions penetration of nanoparticles. Dr. Ryman-Rasmussen commented that the information needed to perform an assessment is a dermal absorption factor; EPA needs to know what percentage of the applied dose is absorbed. It is very difficult to detect nanoparticles and measure their absorption even if they are injected. These particles are only 20 to 100 nm in size, and an average cell can be 50 micrometers (μm) in size. Trying to find them in the whole body is almost impossible.

Dr. Lebowitz noted that there may be ionic transformation of the particles. Even the skin pH is likely to dissolve the particles. The examination is of risk assessment based on Zn, and it does not matter whether it is ionic or nanoparticle. It may be that the blood and urine results are underestimates because of the tendency of the organs to store the Zn. In spite of some deficiencies in the study design, these data are likely to be useful in EPA's risk assessments.

Dr. Popendorf commented that he was hearing some opinions about the validity of the assumption that the Zn was absorbed through the skin. He expressed concern about the potential for hand-to-mouth exposure, which was not addressed. The potential for contamination of the hands is strong. There has been inadequate consideration given for the whole result if contamination occurred. Dr. Chambers mentioned the lack of a control group. The Zn ratios over time were examined in the literature on one person and found an average month-to-month variation of 0.6 percent. Lack of a control group or any estimate of the month-to-month variability of Zn in the subjects limits the validity of the study. The authors had precise laboratory methods, but the field work was rather unsatisfactory. Body weight needs to be taken into account. Additionally, there are several studies referenced that discuss isotope fractionation, which is the tendency of one isotope to be more or less readily absorbed, and the Gulson data included the data of the subjects before exposure, and their ratios were different from the natural background. The issues of hand-to-mouth contamination and the lack of a known change over time are the most serious weaknesses.

Dr. Johnson asked how researchers protected other parts of the body. Dr. Philpott responded that a non-zinc sunscreen was used.

Dr. Manautou noticed that after the sunscreen was applied, a tape stripping method was used to analyze the shape and integrity of the nanoparticles. Dr. Ryman-Rasmussen responded that this was conducted in the pilot group to determine the distribution of the nanoparticles on the surface of the skin to ensure a uniform distribution. Dr. Manautou asked whether a similar method could have been used after the 30 minutes of exposure to determine how much Zn is released after that period. Dr. Ryman-Rasmussen noted that if they had done tape strips on the skin after wiping with the alcohol wipes, this is a repeated dose exposure, so they would risk compromising the barrier for subsequent parts of the study. The only way they could have quantified the amount of sunscreen that was removed from the skin with the alcohol lanolin wipes would be to try to extract the sunscreen. Dr. Manautou noted that an alcohol lanolin wipe would affect the integrity of the material that remains on the skin after exposure. He asked about the EDTA in the sunscreen. Dr. Ryman-Rasmussen noted that it was in the sunscreen as a preservative, but it is possible that if there is Zn released from the nanoparticles, the EDTA could chelate the Zn ions. This is a common formulation for a nano-oxide based sunscreen.

Dr. Philpott agreed that this was not a well-controlled study. Therefore, given all of the caveats in terms of the lack of controls, the possibility for considerable variations over time, and overlap of the particle size, the Agency is asking only about absorption of ZnO.

Dr. Chambers suggested that if it is viewed as a pilot study, knowing that there are tremendous limitations in the design, the data are probably reliable.

Dr. Sharpe questioned how EPA would use something that is called a pilot study differently from a completed study. Dr. Ryman-Rasmussen responded that it would not be relied on solely but would be used as part of the weight of evidence with other data. This is the only study on ZnO that quantifies it in vivo. Some studies have been published that utilize human skin in vitro with ZnO, but the Agency's opinion for pesticides is that in vitro dermal absorption studies have not been sufficiently validated to rely on solely for risk assessment. Dr. Sharpe

asked, in terms of weight of evidence, how would EPA combine information from in vivo and in vitro studies. Dr. Ryman-Rasmussen responded that EPA would look for consistencies in the data in terms of whether there is any evidence of absorption and relative magnitudes of that absorption. If the Gulson at al. study is considered by the HSRB to be a pilot, EPA would likely introduce in vitro data to support the findings.

Dr. Philpott noted that the HSRB was being asked specific questions about the study, and the weight of evidence is beyond the scope of the charge questions presented to the Board He commented that he was hearing that the Board felt that the answer to the first charge question was "yes, but just barely" with a large number of caveats that need to be taken into consideration regarding whether the data are scientifically sound and reliable. The Agency has the message from the Board that the study cannot be used as a stand-alone study.

Dr. Popendorf commented that if the Board determined that the data are reliable, it could be said that the numbers, not their meaning, are reliable. Dr. Philpott answered that the response could be phrased that way, stating that "these data, given all of the limitations of the study and all of the possible factors that may have affected them and how they will be interpreted and used, are nevertheless reliable for consideration in the overall weight of evidence analysis."

Dr. Manautou clarified that the Board must make a statement on the reliability of these data from a study that has improper controls. Dr. Philpott responded that this was correct.

Dr. Lebowitz remarked that the Board was focusing on minutia. Part of the problem is in the wording of the charge question. The study can only be called a study of Zn absorption with limitations. Dr. Chambers added that if the HSRB deemed the study unreliable, it likely would be beyond consideration for EPA, and it might provide some insight to make some decisions along with the other available studies.

Dr. Popendorf mentioned a statement about the sample before exposure, but the number used does not apply to a change over any period of time.

Dr. Philpott stated that the response to both charge questions is "yes, with many caveats and many limitations of the data." EPA should be allowed to use these data as part of the overall weight of evidence but not as a stand-alone set of data to assess the absorption of ZnO through the skin. Caveats will be listed in detail in the final Board report.

Board Ethics Review

Dr. Sharpe commented that because this is the first article that has been submitted since the Human Studies Rule was published, it might be useful to think about how the Board could respond to the charge question relative to this study. Most of the information that the HSRB has about the study lacks supporting documentation. The judgments made, then, are largely inferential. There is no reason to believe that the reported research is fundamentally unethical, but in the absence of an informed consent form and research protocol, there is no documented evidence that pregnancy testing was conducted, participant selection was voluntary, and/or participants understood the nature of the research or their right to withdraw from the study. It can

only be inferred that those requirements were satisfied because of institutional review board (IRB) approval and some other evidence. Does inference meet the "adequate information" standard? The Board has information about the risks being low and mitigated by UV-protective clothing and a trained phlebotomist who drew participants' blood. The research was approved by an IRB-like process, researchers attested that no women were pregnant, and subjects were allowed to cease participation. There is no evidence, however, beyond that attestation of the researcher that no women were pregnant. There also is no information about the pilot study, no documented evidence that pregnancy testing was conducted, and no knowledge that subject selection was voluntary. It is unknown whether subjects were related to the researchers, risk-benefit information was sufficiently communicated, and medical treatment was available and provided to subjects. The risk is very low, and if the Board uses a sliding scale, the threshold for adequacy should be understood in proportion to the risk.

Dr. Northington Gamble stated that the answer to the charge question is "no, there is not adequate information" for many of the reasons that Dr. Sharpe outlined. She finds it problematic to use inference as a conceptual model but agrees completely with Dr. Sharpe's findings. If the Board uses inference without any documentation, that is a "slippery slope." The HSRB does not have documentation of pregnancy tests, although eight out of the 10 women were premenopausal. There is no documentation of the consent forms and their contents. There is no discussion of coercion in terms of power dynamics. There are too many "red flags," and without additional information, there is not adequate information to support the ethical conduct of this research.

Dr. Manautou asked whether the Agency requested an informed consent form from the authors. Ms. Parsons responded that she had asked, and Dr. Gulson believed that she was asking for the signed consent forms. The response she received from the ethics secretary stated that the documentation for the ethics signoff was adequate.

Dr. Philpott mentioned that it was important to note that subpart L forbids EPA to use data that involve intentional exposure of pregnant and nursing women and children to these compounds but does not require demonstration that women are not pregnant or nursing. Therefore, the fact that a pregnancy test was not conducted does not mean that regulatory obligations were not met. The onus is on EPA to provide the HSRB with enough data for the Board to be confident that the study was conducted in compliance with regulations as protective as those in the United States. The Board's consensus seems to be that the answer is the "information is not yet adequate."

Dr. Chambers questioned whether the regulations only applied to pesticides. Dr. Philpott responded that it fell under 40 CFR part 26, so it was under the same regulation. Mr. Jordan noted that the applicable regulation was 40 CFR §26.1703, which prohibits a study conducted with children or pregnant or nursing women. That particular section does not contain an evidentiary standard, as Dr. Philpott noted. Subpart L applies to studies that are conducted with the intention to submit them to EPA, so it does not apply to this study. The §26.1703 standard was satisfied. The second piece of analysis is whether the standard in §26.1705 was satisfied, which means that EPA must have evidence that the study was conducted in substantial compliance with procedures at least as protective as EPA's regulations. If it is concluded that

standards in Australia are as least as protective as those in the United States, the next question becomes whether this study was conducted in substantial compliance with the Australian requirements. Dr. Philpott noted that the Board was in agreement that the Australian standards were as protective as those in the United States, but the question is whether adequate information to support its compliance with those standards is available. He added that with the pre-rule studies, the Board talked in detail about evidentiary standards and what would have to be shown to state that the study was not performed in substantial compliance with applicable regulations.

Dr. Sharpe noted that the Board can provide EPA with a list of the kind of information that would be useful. The HSRB is asking whether the study received IRB approval for reasons that would allow the Board to assess whether that approval was appropriate. The HSRB does not want to set a bad precedent for reviewing post-rule literature. She suggested using the HSRB's recommendations to request the informed consent form and any research proposal that is available from the university that approved the study or the researchers. Dr. Philpott added that the Board did not believe that its answer to the charge question would always be "no," but that the answer was "not yet."

Dr. Johnson asked if the Board would produce a list of items needed to make the decision. Dr. Philpott suggested that the HSRB make a list of documents that members would like to see.

Dr. Northington Gamble stated that Dr. Sharpe should be applauded for delineating what was and was not adequate in the current information. She agreed that the answer was "no, not yet" in terms of having adequate information.

Dr. Lebowitz inquired whether some questions of clarification on the scientific issues also could be asked when the Agency queries Dr. Gulson for information on ethics. Dr. Philpott responded that if this was provided, perhaps all of the charge questions could be reconsidered. That is a fairly large undertaking but not inappropriate. EPA would be welcome to bring further scientific information back to the Board, but ethics information is needed. Dr. Ryman-Rasmussen asked what additional information would be needed. Dr. Philpott responded that there was a list that could be e-mailed to Dr. Ryman-Rasmussen and Ms. Parsons.

Dr. Chambers asked whether the science charge questions would be revisited. Dr. Philpott answered no, unless the Board was asked to do so. The answers to the first two charge questions stand. If EPA receives additional scientific information on which it would like HSRB input, the issue can be revisited by the Board. Dr. Chambers noted that the Board's concerns were with the design of the experiment. The Board likely has judged the science as well as it can.

Dr. Sharpe questioned whether the Board would be identifying what would count as adequate information. Dr. Philpott answered that the Board should try to identify some of the elements that lack adequate information but not identify particular documents that need to be submitted. If members have lists of specific concerns that need to be addressed to have adequate information to determine whether the study was conducted in accordance with procedures that are as protective as EPA's regulations, submit them to Dr. Philpott. If the Board could give Ms. Parsons some suggested starting points during that day's meeting, it would be useful. Dr. Sharpe

would like to request the informed consent forms and the study protocol. She also would like to see information from the IRB's deliberations. Dr. Northington Gamble asked for a response to a letter sent to Mr. Herbert Wong (Graduate School of the Environment, Macquarie University) in January 2006 from the research ethics officer, Kokila De Silva, because in that letter, the question was raised about the volunteers.

Dr. Philpott reiterated that the Board's consensus as to whether or not there is adequate information that the Gulson et al. study was conducted in substantial compliance with procedures that are at least as protective as existing EPA human subjects protection regulations is "not yet," and the Board suggested that EPA obtain some additional information such as the informed consent document, study protocol, and any IRB recommendations including Dr. Gulson's and Mr. Wong's response to the question about whether the volunteers were colleagues or students of Dr. Gulson. This is the Board's first review of a post-rule published study, so the fact that the HSRB is not finding it in compliance should not be seen as a failure on the part of the Agency or the researchers.

Session 3: Reconsideration of Two Concerns Previously Raised by the HSRB in Its June 2009 Review of an Intentional Human Dosing Study with Chlorpyrifos (Kisicki et al. 1999); Additional Pertinent Information Was Made Available by the Sponsor Related to These Two Concerns

Dr. Philpott explained that this reconsidereation of two concerns previously raised by the Kisicki et al. study was not coming to the Board from the Agency. Rather, the new information was raised at a recent FIFRA SAP meeting. This study was discussed at the June 2009 HSRB meeting. The Board reviewed three pre-rule studies at the meeting that examined human exposure to chlorpyrifos: the Nolan study from 1984 that measured the absorption, distribution and excretion of chlorpyrifos; the Honeycutt study from 1992 that examined agricultural worker exposure to chlorpyrifos with field re-entry; and the Kisicki study from 1999 that determined the no observed effect level as measured using red blood cell (RBC) acetylcholinesterase inhibition for chlorpyrifos.

The Nolan study included six male subjects who received an oral dose of chlorpyrifos as 0.5 mg/kg in tablet form and a 5.0 mg/kg dermal dose. The endpoints being measured were RBC cholinesterase inhibition (ChEI), plasma ChEI, blood 3,5,6-trichloro-2-pyridinol (TCP) levels and urine TCP levels. In comparison, the Kisicki study was comprised of 30 male and 30 female subjects, with 12 per sex as controls and six per sex per dose group. The doses included 0.0, 0.5, 1.0 and 2.0 mg/kg in capsules, and the endpoints examined were RBC ChEI, blood TCP levels and urine TCP levels.

The Board was asked whether the blood and urine measurements of chlorpyrifos and/or TCP from the Kisicki et al. oral study were reliable, and it had many concerns. The HSRB responded that questions about the analytic procedures used, the lack of an appropriate gluconamide control, and apparent discrepancies in the absorption data when compared with the data from Nolan et al. raised concerns about the reliability and utility of these data for risk assessment purposes. The concerns about the reliability and validity of the Kisicki et al. data included whether the urine samples were subjected to acid hydrolysis before processing and

quantifying the chlorpyrifos metabolite TCP and why the absorption of chlorpyrifos was so much different than in a study of chlorpyrifos by Nolan et al. (35 percent versus 70 percent respectively), calling the analytical methods of Kisicki and his colleagues into question. Acid hydrolysis is necessary to hydrolyze the gluconamide conjugate of TCP and liberate the metabolite for analysis, and whether Kisicki et al. performed this step could not be determined from the materials that were presented to the Board at the 2009 HSRB meeting. Because the urine TCP data were being used in the analysis and to examine the relative absorption of chlorpyrifos, it raised significant concerns. If acid hydrolysis was not used, it could explain the difference between Kisicki et al.'s findings and what was seen in the Nolan study.

The Dow Chemical Company (Dow) provided new information to the Agency at the FIFRA SAP meeting that addresses the procedure used for analyzing the urine and explores the differences between the tablet and the gelatin capsule formulations that explain the difference in absorption. Therefore, the difference in absorption may not bring into question the analytical methods used by Kisicki et al. and may be because of the difference in formulation.

Dr. Manautou inquired whether the analytical method measures free TCP. Dr. Chambers responded that the analytical method is for free TCP and would not detect gluconamide conjugate of TCP. Dr. Philpott noted that the HSRB had other concerns, such as total mass balance and questions about participants in the study, but those are not at issue. The questions to reconsider are those about the urine sample being subjected to acid hydrolysis and whether there is a better explanation for the difference in the absorption in the Kisicki versus Nolan studies other than calling into question the analytical methods used. The Board now has additional information provided by Dow to the Agency that raises questions about whether the concerns that are written in the June 2009 final report, a publicly available document, now are moot.

Questions for discussion include:

- Do the recommendations provided by the HSRB at its June 2009 meeting and in its subsequent report regarding the reliability of data on the urinary metabolite trichloropyridinol in the Kisicki et al. (1999) study change in light of the new information provided?
- Do the recommendations provided by the HSRB at its June 2009 meeting and in its subsequent report regarding the level of absorption of chlorpyrifos in the Kisicki et al. (1999) study change in light of the new information provided?

Dr. Chambers stated that Dow was asked specific questions later in 2009 and provided some information to EPA, but that information was not shared with the HSRB. At the February 2011 FIFRA SAP meeting on chlorpyrifos, the HSRB report from the June 2009 meeting was part of the documentation. Dow scientists pointed out that they had answered those questions and produced a document that was delivered to the SAP. If the HSRB had received this information prior to finalizing its report, the recommendations might have been different. The Nolan and Kisicki studies are linked because the HSRB was concerned that the methods description in the Kisicki study indicated that the blood was acid hydrolyzed to free the TCP, but the description of the urine methodology did not describe acid hydrolysis. If it was not conducted, that could have been part of the difference between the absorption in the two studies at the same dose. The

explanation at the time that the gelatin capsule took longer to dissolve and absorption was therefore lower did not seem adequate to the Board. Dow's document states that the acid hydrolysis method used in the study was the same as in the Nolan 1987 rat metabolism study. With respect to the absorption, the Board did not have sufficient information at that time to indicate the form of the chlorpyrifos that was administered to those in the Nolan and Kisicki studies. In the Nolan study, in which there was 70 percent absorption at the 0.5 mg/kg dose, the chlorpyrifos material was dissolved in methylene chloride, and the resulting solution was applied to a lactose tablet. In contrast, in the Kisicki study, the chlorpyrifos material was formulated by weighing a crystalline test material into a gelatin capsule and filling the remainder of the capsule with lactose powder. These were much larger particles of chlorpyrifos than in the Nolan study. The difference in formulation is sufficient to say that a difference in the absorption would be expected between the two studies.

Dr. Philpott noted that the Board now could have a discussion about whether to amend the June 2009 recommendations. Dr. Chambers stated that Dr. Michael Bartels from Dow was present and could answer any questions of clarification.

Dr. Manautou asked whether the different formulations would bring sufficient difference in dissolution rates to explain the magnitude of differences in absorption between the two studies. Dr. Chambers responded that she did not know if that was the case, but it is more logical knowing that the formulation is that different.

Dr. Lebowitz commented that the evidence presented could indicate that smaller particle sizes could be absorbed better, but the sizes of the particles are not known. Dr. Philpott explained that at the June 2009 HSRB meeting, the Board stated that it did not believe that the differences between the formulations could explain the differences in absorption and raised concerns about the analytical methods used. The additional information suggests that it might explain the differences in absorption.

Dr. Chambers read the statement that the Board had made at the June 2009 meeting: "Kisicki et al. suggested that the oral absorption is slowed by the dissolution of the gelatin capsule with the concurrent reduction in the total amount absorbed." Although the Board agreed that absorption of chlorpyrifos from the gelatin capsule might be slower than that from the lactose tablet, there was some skepticism that the difference in dosage form would yield this large discrepancy in total percent absorbed in the two studies. She noted that the Board now had other information about what might have contributed to the difference in that same dose level in the two studies.

Dr. Green asked about the lactose in the capsules. Dr. Chambers replied that it was not bound to the crystalline chlorpyrifos.

Dr. Popendorf noted that it was the crystals within the capsule, not the capsule itself, making the difference in absorption. Dr. Chambers stated that this was correct, but the report indicated skepticism that the gelatin capsule would have taken long enough to dissolve to account for the difference. She added that the difference seems to be real with the new information taken into account. Dr. Popendorf commented that the Board wanted to say

something new, not change what had been said in 2009. Dr. Philpott answered that any change would amend the 2009 report to say, "in light of information that the Board did not have at the time, some of these concerns no longer are valid."

Dr. Manautou questioned whether the differences in absorption defined by blood levels at a given time were indicated in the two studies. Dr. Chambers answered that the Board's concern had been with the urine levels. Dr. Manautou asked whether chlorpyrifos undergoes antihepatic circulation, and the lactose could be converted in the intestine to lactic acid. Dr. Chambers replied that there is lactose in both formulations. Dr. Philpott added that there was a real discrepancy because both the Nolan and Kisicki studies had a 0.5 mg/kg oral dose, and the urine TCP data was very different in each. This led the Board to determine that there were some methodological problems with the Kisicki study. Some of those concerns appear to have been addressed with the information that Dow provided to the Agency.

Dr. Chambers asked Mr. Bartels if she had misrepresented anything in the study. Mr. Bartels stated that Dr. Chambers had described the supplementary information appropriately. The methods used in the Kisicki study are well described in another report that was submitted to the Agency, and he has the master record identification number if that is needed. In the Kisicki study the methods used, as Dr. Chambers described, were identical to those used in many prior studies. The TCP can be measured directly once the conjugate is treated with acid. In this study, the laboratory conducted repeat analysis of selected samples and extended the hydrolysis time for another 2 hours. The bioavailability of the absorption is most easily analyzed by examining the urine levels. In the document provided to the Agency, Dow listed several examples of moderate changes in particle size giving a two- to four-fold increase in absorption.

Dr. Lebowitz inquired about the particle size used by Nolan and by Kisicki. Mr. Bartels responded that those measurements were not taken, but the material in the Nolan study was dissolved in a small volume of methylene chloride and applied as a solution to a tablet. That would be a very small particle size with very large surface area to mg of test material. In the Kisicki report, there is documentation that the material used was a crystalline solid; there was no further milling of the material beyond what was generally done to prepare this kind of product. When animal toxicology studies are performed, Dow routinely takes white crystalline solids and further reduces the particle size to obtain homogeneous preparations.

Dr. Popendorf asked, if the Board accepts the fact that the data from Kisicki show one-half of the absorption of the Nolan data, then the dose in the Kisicki study is one-half of what was absorbed in the Nolan study. Mr. Bartels responded that this was correct, and that conclusion was put forward in a publication in 2002 using the Nolan and the Kisicki data.

Dr. Chambers noted that reevaluating and interpreting the data were not the point of the discussion. If the Board's recommendations would have been different in light of this new material when the report was written, should the Board amend the report so that the record is corrected? Dr. Philpott added that the Board is not correcting anything nor reevaluating the Kisicki study. The question is whether the Board should amend its recommendations to be less skeptical in terms of the acid hydrolysis and the explanation of the difference in absorption. The analytical methodology probably was appropriate. The difference in formulation does not

necessarily explain the entire difference in absorption between Kisicki and Nolan, and the Board can consider whether it wants to say it may have had an effect.

Dr. Young clarified that the Board just was discussing the two affected recommendations. Dr. Philpott confirmed that the other two concerns and recommendations will remain.

Dr. Johnson suggested that the Board should amend the record and asked whether the Board would include a paragraph on this matter in the current report. Dr. Philpott answered that this had not been done before. The proposal is that the Board write something brief about this, and this report will cross-reference the June 2009 report; the June 2009 report on the Web site will link to this report.

Dr. Lebowitz recommended that the Board amend the 2009 report to reflect the new knowledge. It should amend statement number one to say that the difference in formulation of the chlorpyrifos in the two studies may explain the difference in urinary results, and statement two should say that the analytical method was correct. Dr. Chambers suggested that she draft the amended recommendations and present it to the Board the following morning.

Dr. Philpott asked whether any Board member had serious concerns about whether or not the HSRB should amend the June 2009 report. He noted that the consensus agreement was that Dr. Chambers would write brief statements answering these two questions, and the Board would discuss them briefly at the beginning of the meeting the following day. Mr. Downing added that there would be an opportunity at the next teleconference meeting to review the statement. Dr. Philpott stated that he would prefer to get a consensus statement during the current meeting.

Mr. Downing concluded the meeting for the day at 4:35 p.m. He announced that the next day's public meeting would begin at 10:00 a.m., but Board members have an administrative meeting at 8:30 a.m. at which the Board's bylaws would be discussed.

Thursday, April 14, 2011 Introduction and Identification of Members

Mr. Downing welcomed attendees and members to the second day of the HSRB meeting and turned the meeting over to the Chair, Dr. Philpott.

Dr. Philpott thanked the Agency and the Board members for their diligent work in preparation for this meeting and asked members to identify themselves and their affiliation.

Follow-up from Previous Day

Ms. Sherman stated that the regulatory framework discussed the previous day may not reoccur based on the fact that proposed changes to the rule would change the standard applicable to studies such as Gulson that were not conducted by people intending to submit them to the Agency or not conducted under EPA's rules. The current standard is 40 CFR §26.1703, which prohibits reliance on studies involving pregnant or nursing women or children, and 40 CFR §26.1705, which states that EPA needs to have adequate information to determine whether the research was conducted in substantial compliance with standards as stringent as EPA's. The new

standards proposed for these types of research would be §26.1703 and §26.1705, which state that EPA must not rely on data from research subjects if there is clear and convincing evidence that the research was fundamentally unethical or the research failed to obtain informed consent or if the research was deficient relative to the ethical standards prevailing at the time. The thinking was that in holding research to the standard that researchers would not know that they were subject to at the time of the study, good research found in the literature could potentially be eliminated.

Dr. Philpott clarified that the framework under which both the pre- and post-rule studies and peer-reviewed studies would be standardized. Ms. Sherman responded that EPA was adjusting the standard for research not otherwise subject to this rule.

Dr. Northington Gamble asked about the status of the proposal. Ms. Sherman replied that the Agency completed a rulemaking process, and most of the other changes to the rule were a result of a settlement agreement with the Natural Resources Defense Council. The comments received on the proposed rule will be evaluated, and a determination will be made whether adjustments are needed. EPA plans to issue the final rule in December 2011.

Follow-Up to Kisicki et al. Study Discussion

Dr. Philpott noted that the Board had proposed that Dr. Chambers craft some draft language for the Board members to examine, which would be incorporated into a supplement to the June 2009 and the April 2011 final meeting reports and discussed on the next public teleconference meeting.

Dr. Chambers explained that the text she supplied to the HSRB includes paragraphs to inform the reader why the recommendations were reconsidered, but the important part is the final paragraph. The language will be edited before appearing in the final report, but the two critical points decided the previous day were addressed: (1) the differences in absorption between the Nolan and Kisicki studies and (2) the concern about the urinary metabolite extraction.

> "The Board considered this additional information and indicated that its original recommendations on these two points only about the Kisicki study should be amended as follows: (1) it is logical that larger particles of materials such as chlorpyrifos would be absorbed more slowly than smaller particles. The differences in absorption between the Nolan and Kisicki studies may have resulted, at least in part, from the different sizes of chlorpyrifos particles in the two formulations; and (2) the quantitation of urinary TCP was accurate because the urine was subjected to acid hydrolysis and heat to liberate conjugated TCP."

Dr. Chambers added that if there are no major substantive changes to the content, it can be edited before the meeting report is finalized.

Dr. Manautou suggested that the second sentence of the first statement read, "The different sizes of chlorpyrifos particles in the two formulations may have contributed to the

differences in absorption between the Nolan and Kisicki study." Dr. Chambers responded that "may" was included as a caution, as was "at least in part."

Dr. Philpott asked whether the general consensus of the Board was that the difference in particles between the two formulations in the Nolan and Kisicki studies may explain, at least partially, the difference in the absorption. Dr. Popendorf added that the statement made previously that the difference in handling may have contributed to the difference in absorption should be rescinded, and this could be added to the second recommendation. Dr. Philpott suggested addressing within the original recommendation the fact that because the urine was subjected to acid hydrolysis to free the conjugated TCP, the Board no longer believes that differences in handling likely explain the differences in absorption. Dr. Chambers and Dr. Philpott will edit the language and incorporate the text into a draft document that will be sent to the Board members for comment, and it will be discussed during the public teleconference meeting to finalize the April 2011 HSRB meeting report. Dr. Philpott commented that these amendments address only two of four major concerns that the Board has with the Kisicki study.

Session 1: Completed AEATF II Research on Exposure of Professional Janitorial Workers When Wiping an Indoor Surface with an Antimicrobial Pesticide

Mr. Timothy Leighton (OPP, EPA) explained that EPA had reviewed AEATF II research on exposure of workers to an antimicrobial pesticide while wiping indoor surfaces. He noted that EPA's contractor, statistician Dr. Jonathan Cohen of ICF International, was available by telephone to answer any questions. Mr. Leighton explained that the study involved two exposure scenarios: the ready-to-use (RTU) wipe and the trigger spray and wipe.

EPA Science Assessment

Mr. Leighton noted that the Board had reviewed the scenario for this study in April 2008. The wipe studies were conducted at the same time as the AEATF II mop study that was reviewed in October 2010. Therefore, the lessons learned from the mop study are not incorporated. Individuals wiping indoor surfaces are being monitored, and pouring the concentrate into the trigger spray bottle was excluded because this can be conducted in a variety of ways and will be examined as a separate scenario.

The RTU wipes come in an 8.5" x 5" cylindrical container that contains 75 wipes. There is roughly one-half a liter of diluted production (0.04 percent ai) in the wipes, or approximately 2.5 mg of didecyl dimethyl ammonium chloride (DDAC) per 8" x 7" wipe. Subjects used up to 250 wipes in a monitoring event (ME). The trigger spray is a 32-ounce container with a trigger and rag used for wiping.

The locations of the study were three randomly selected vacant buildings in Fresno, California, the same sites as the previously conducted mop study, with each subject only monitored once. To ensure the diversity of individual exposures, at each site one enrolled subject was assigned to each of six MEs, defined by the planned duration of wiping. The maximum duration was 120 minutes; the Board had suggested that this was too short of a time period, and it was increased to 210 minutes. All but one study participant was within 1–2 minutes of the

timeframes. One at the higher timeframe was only 165 minutes instead of 180 to 210. There were six subjects at each of three sites (n = 18) exposed to DDAC. Subjects wore WBDs and breathing zone OVS air samplers and wiped as they normally would with the RTU wipes in one scenario and a trigger spray and wipe in the second scenario.

The wipe protocol's stated objective was to "…sample estimates of the arithmetic mean and 95th percentile of normalized exposure are accurate to within three-fold 95 percent of the time." Both EPA and AEATF II II recognize that drawing statistical inference from the results of the purposive sampling design to the universe of people wiping is not statistically justifiable. EPA asked the AEATF II to specify the type of wipe/rag in the trigger spray and wipe scenario (cotton rags from Bag-o-Rags) and provide data on recovery efficiency of hand-wash/face-wipe methods for DDAC (provided existing study on efficiency of DDAC residue removal from hands). The HSRB asked the AEATF II to consider repeat measurements, but there is a tradeoff of knowledge about within-worker variability for more samples of between-worker variability. The HSRB suggested longer monitoring duration, and based on industry information, maximum monitoring time was increased. The HSRB recommended that the AEATF II consider defining ME by AaiH rather than duration, but the best information on wiping was by duration. Finally, the HSRB suggested a review of proportionality between exposure and AaiH, which EPA itself conducted.

Protocol deviations were similar to the mop study. There were 23 deviations reported, none of which negate the use of the exposure results. The same hand residue removal efficiency study used in the mop study was employed, but the wipe study hand wash and face/neck wipe procedures are similar. The WBD was used inside and outside, and each body part was analyzed. The same three clothing configurations presented in the mop study were used. For the scenarios, people worked as they normally did; people using the RTU wipe wiped up to 5,030 square feet and used from 27 to 250 wipes in an ME, with an average use of 127 wipes. The trigger spray use averaged just less than 0.5 gallons. The area wiped was slightly less than with the RTU wipes, and the maximum area wiped was 3,629 square feet. The concentration of spray used was roughly the same as the amount in the RTU wipes. DDAC was used because it has a sensitive method, and the LOQs are very low. The controls showed that everything was less than the LOQ, and there were no contamination issues. The laboratory and field recoveries were good, and the field recoveries were used to correct the field samples.

In terms of statistical analysis, three methods were used to estimate unit exposures: empirical estimates, a simple random sample and a mixed model. The mixed model was selected to best represent the unit exposure results. In the mop study, one of the Board members suggested examining the quadratic model, degrees of freedom and the nonparametric bootstrap, so Dr. Cohen conducted those three analyses. He conducted the same procedures with the wipe study results.

The fitted mixed model results were used to examine inhalation, with the results provided as mg and mass per ai. Comparing the two scenarios, dermal exposures are higher with the RTU wipes. The inhalation with RTU wipes, conversely, is much lower than the trigger spray. All of the RTU hand exposures were greater than the LOQ, and 12 of the 18 air samples were detectable. Most of the inner dosimeters were non-detects, and the outer dosimeters were

detectable. For the trigger spray, all of the hands and face levels were greater than the limit of detection. Most of the inner dosimeters were less than LOQ, and of the outer, only two were less than LOQ.

The benchmark objective of three-fold relative accuracy was met for the mixed-model results using the "3 cluster x 6 ME" study design, so no additional MEs are needed; the sample was large enough to satisfy EPA's needs. Proportionality between exposure and AaiH is an assumption EPA uses in handler exposure assessments, and the results of most scenarios are expected to show an increase in exposure with an increase in AaiH. The wipe data are consistent with the assumption of increasing exposure with increasing AaiH, except inhalation exposure for the RTU wipes, which showed no evidence of a positive relationship between RTU inhalation exposure and AaiH. The unit exposure for RTU wipes, using the slope of the regression of the log exposure against the log ai, was 2,400 mg per pound (mg/lb) ai, which is the RTU threshold.

In terms of limitations on the data generalization: the wipe study population is not a true random sample; statistical inference from these results to the universe of people wiping is not justifiable; and surrogate assessments applying less than the threshold of AaiH will underestimate exposure, whereas AaiH greater than the threshold will overestimate exposure. EPA's plan for the data is to use unit exposure data generically to estimate potential exposure to low- or moderate-volatility pesticides used in wiping scenarios and to use chemical-specific hazard and dermal absorption data to estimate internal dose and risk.

In conclusion, study results are sufficiently sound to support estimates of dermal and inhalation unit exposures in the two wiping scenarios, an adequate number of samples were collected, and data limitations must be acknowledged in the risk assessments.

Board Questions of Clarification—Science

Dr. Young asked whether slide 26 of EPA's presentation showed log exposure and log ai, because it is labeled exposure and ai. Dr. Cohen answered that the purple line was calculated using the unit exposure or exposure lbs AaiH. Dr. Johnson remarked that he thought the model was fit on the log scale but demonstrated on the non-log scale. Dr. Cohen responded that this was correct.

Dr. Lebowitz examined the report and slides, and per unit exposure does not appear to correspond with Tables 2 and 7, but there may be an explanation for this. The numbers do not correspond. Mr. Leighton replied that Table 1 is a summary of the mixed model results, and Tables 2 through 7 report the empirical results. Results of this study are similar to the previous wipe studies. Dr. Lebowitz asked, with all of the non-detects in the new study and the LOQs, if EPA is saying there is no effect. Mr. Leighton responded that in the mop study, the same conversation was held, and EPA re-examined whether it should be using something other than one-half of LOQ for non-detects. Based on the percentage change in the results, it was decided not to do anything different. Dr. Lebowitz inquired whether the non-detects were included as zero or one-half of the LOQ in the different regressions. Dr. Cohen responded that one-half of the LOQ was used for the non-detects. Dr. Lebowitz noted that all of the dermal exposures were combined, and because there were so many non-detects, the hand became the most important

because there were no non-detects in this measurement. Therefore, what is shown in the regression is almost entirely from the hand. Dr. Lebowitz noted that this needed to be stated more clearly in the results. He stated that he had found a fair number of non-detects and deviations in the fortified samples. He asked whether in the analysis of quality assurance/quality control, the large number of exceedances of the fortified samples and deviations would affect the results of the study. Dr. Lebowitz questioned whether EPA thinks that by correcting the samples for the actual results of the fortified samples that this problem has been addressed so that there is no bias. Mr. Leighton stated that was correct.

Dr. Lebowitz asked why EPA thinks a regression slope of 0.5 is important. Mr. Leighton responded that the lower the slope when EPA's equation is used, the higher the overestimate of exposure. Dr. Lebowitz asked if the regression is 0.25, whether EPA still would use that as extrapolating from unit to the lbs ai. Mr. Leighton replied that there was additional uncertainty, but it still would be used.

Dr. Lebowitz questioned why the nonparametric bootstrap would be excluded when the CI was even narrower than with the parametric. Dr. Cohen stated that both had been presented. Dr. Lebowitz commented that EPA had decided to ignore the nonparametric results or revert to using the parametric. Mr. Leighton commented that perhaps this could be added to the discussion within the review. Dr. Lebowitz noted that in Table 7, a great amount of variability is shown among the cluster results. How did EPA determine to combine results from different clusters when one cluster might have results that are twice or one-half as great as the others? Mr. Leighton answered that variation between the clusters could have to do with the amount of wipes, or ai, used. This could be examined among the clusters.

Dr. Fernandez noted, on slide number 10 of EPA's presentation, that under the study objective it only states the estimates of arithmetic mean and the 95th percentile of normalized exposure. He assumed that these analyses had been conducted based on log-transformed data. Mr. Leighton said that geometric mean also had been calculated. Dr. Fernandez stated that it looked as though the data had not been transformed based on normal distribution. Is the data coming from log-transformed data and then adjusted for the arithmetic mean? Dr. Cohen answered that this was correct. Dr. Fernandez noted that the main concern is the upper limit, so why should EPA be concerned about including the lower limit? Mr. Leighton stated that he was correct, and the process could be streamlined by only examining the upper 95th percentile.

Dr. Popendorf asked about chronic versus acute exposure. Mr. Leighton responded that in EPA's assessments, if examining a chronic exposure, the Agency would not be using the 95th percentile. The 95th percentile is to examine a 1-day, short-term effect. The Joint Regulatory Committee wanted to examine all of the statistics within the study, so even if the arithmetic mean is used, EPA still wants to be able to report the 95th percent confidence limits.

Dr. Fernandez asked, regarding slide number 19, if the recovery percent was for the three clusters, and why there was more than 100 percent recovery. Mr. Leighton responded that the percent was for the three clusters, and the figure was greater than 100 because sometimes x amount is fortified on a patch, and if it comes back as 109 percent, that is the range of the

analytical technique. EPA does not correct anything that is above 1,000 percent. Corrections are made upwards but not downwards.

Dr. Popendorf asked how long the material was on the skin in the hand removal efficiency study referenced in the report. Two levels of exposure were tested, but the time on the skin was not reported. Mr. Leighton replied that after it was fortified on the hand in the removal efficiency study, it was allowed to dry for 30 minutes.

Dr. Philpott invited Dr. Has Shah (AEATF II), Dr. Robert Testman (Golden Pacific Laboratory) and Ms. Megan Boatwright (Golden Pacific Laboratory) to answer Board questions.

Dr. Popendorf noted that the instructions to subjects stated that subjects were advised not to re-wipe any surface during the given ME and wondered what was intended and how this instruction was interpreted. He asked how the applicators figured out how much wiping they were supposed to do and how much ai they should use. Dr. Testman answered that the subjects were asked to do their job as they normally would, but they were to wipe new surfaces continually rather than going back over surfaces. Mr. Leighton added that the Joint Regulatory Committee (EPA, Health Canada, and California) asked for the same method. Originally, this study was going to be performed in the laboratory, but it was decided that there would not be enough surface area.

Dr. Popendorf added that the study described the subjects as having both training and experience, and he asked what sort of training the subjects have. Dr. Testman answered that it would be considered on-the-job training. Researchers did not provide any training but did screen subjects to ensure that they had janitorial experience and had wiped surfaces professionally. Dr. Popendorf asked how the workers knew when they had cleaned enough. Dr. Testman responded that it was largely left to their discretion to clean as they would in their day-to-day job. Dr. Popendorf questioned if there were similar levels of wetness that resulted from the cleaning or distinct differences among the subjects. Ms. Boatwright replied that variability could be seen from person to person, but within-person results were fairly consistent. Mr. Leighton added that square foot wiped per minute could be examined in the review. When this information is used to label a product, the label will state only "wipe surfaces," not how to wipe.

Dr. Philpott thanked the sponsors and noted that they would be given a chance to make a public comment later in the meeting. Dr. Shah stated that Dr. Sami Selim had resigned from Golden Pacific Laboratory and Dr. Testman has taken over.

<u>EPA Ethics Assessment</u>

Ms. Sherman noted that the protocol was reviewed in April 2008, the recruiting and subject enrollment occurred in April to July 2009, and the field monitoring took place in 2009. The comments and input on the mop study were reviewed in October 2010 and, therefore, have not been applied to this research. The report was submitted to EPA in January 2011.

Recruiting initially followed procedures in the protocol, but this proved unproductive. The protocol was amended to allow subjects to be recruited and enrolled as they came forward

and further amended to allow recruiting through newspaper advertisements. An advertisement was approved by IIRB and appeared in three newspapers in the Fresno, California area. Ms. Sherman found that the recruiting process was equitable and free of coercion or undue influence.

In one unreported deviation, three subjects reported that they were in "fair health." This was contrary to the protocol, which stated that subjects should be in "good health" to participate. This issue was discussed at the October 2010 HSRB meeting, and the conclusion was that this deviation did not render the results unacceptable, but the HSRB and EPA recommended that the AEATF II in the future clarify the criteria used to establish health status. Only one of these subjects was monitored; the others were alternates.

Thirty-six subjects were monitored, of which 20 were male and 16 female; 33 were English-speaking, whereas three were Spanish-speaking. The mean age was 42.8 years, with 13.5 mean years of experience; 72 percent requested to receive their exposure results.

Four instances of a subject speaking to the medical professional or reporting feeling ill occurred, possibly as a result of inhaling fumes. In all of these cases, the subjects continued working, and none of these situations resulted in an adverse event. One subject left early because he was feeling ill, but it was not reported whether his illness was related or unrelated to his participation in the study. The subject that reported fair health was not one of these five subjects.

Ms. Sherman believed that the AEATF II was successful in responding to EPA and HSRB comments in the protocol review process.

The initial protocol was reviewed by the IIRB in January 2008, with a revised protocol incorporating comments from the HSRB and EPA approved by IIRB in February 2009. Eight amendments were approved during the course of the study, and two deviation reports included 23 deviations from the protocol.

The deviations that were important from an ethics standpoint included two reported deviations: some subjects omitted or shortened rest breaks, and there were photographs showing subjects' faces taken at one monitoring site, but none of these images were included in the report. The unreported deviation was the aforementioned enrollment of subjects with self-described fair health.

The documentation that EPA received from the AEATF II was complete and well indexed, and the ethics portion was thorough; requirements of 40 CFR §26.1303 are satisfied.

Substantive acceptance standards include 40 CFR §26.1703, which prohibits reliance on data involving intentional exposure of pregnant or nursing women or of children; 40 CFR §26.1705, which prohibits reliance on data unless EPA has adequate information to determine substantial compliance with subparts A through L for 40 part CFR 26; and FIFRA §12(a)(2)(P), which makes it unlawful to use a pesticide in human tests without fully informed, fully voluntary consent. EPA found that all subjects were at least 18 years of age; pregnant or nursing women were excluded; all females were tested for pregnancy; there were no noteworthy deficiencies in the ethical conduct of the research; the protocol was faithfully executed and amended when

needed; minor deviations did not compromise safety or consent of subjects; and subjects were fully informed and their consent was fully voluntary, without coercion or undue influence.

In conclusion, available information indicates that the AEATF II II Wipe Study was conducted in substantial compliance with subparts K and L of 40 CFR part 26.

Board Questions of Clarification—Ethics

Dr. Northington Gamble stated that regarding responsiveness to HSRB comments, Ms. Sherman noted two instances in which they were not addressed. One related to the purpose of the study that would be to collect information to be provided to EPA, and the second related to the flyer's notation that it would measure inhalation as well as dermal exposure. Dr. Northington Gamble questioned why these issues were not addressed. Ms. Sherman responded that she did not have additional information.

Drs. Shah and Testman and Ms. Boatwright responded to questions from the Board. Dr. Northington Gamble asked about follow-up on the subject who left early because he was not feeling well, and it was unclear whether that was because of the research. Ms. Boatwright answered that the subject had reported to the study stating that he was not feeling well, but that he wanted to participate in the study. Dr. Northington Gamble stated that she was referring to the subject who left early, RTU wipe cluster 3, W39. Dr. Philpott stated that the change in participant numbers was difficult to follow, so perhaps in the future, participants can receive one number for the entire study. Dr. Testman responded that he would have to look at the study notes and would follow up through EPA.

Dr. Northington Gamble noted that the HSRB had recommended that the recruitment flyer note that inhalation as well as dermal exposure would be measured, but there was no change in the flyer. Dr. Testman responded that he would have to follow up on that subject as well. Dr. Northington Gamble stated that the matter of stating what EPA would use the data for on the consent form also was not addressed and asked for information on this as well.

Dr. Popendorf commented that the field notes contained notations such as "+1" and "+6" and asked what this referenced. Ms Boatwright answered that one of the observers used the notation to note how many times a subject performed an action.

Dr. Philpott stated that in Ms. Sherman's review, it is noted that an IRB-unapproved form was used to collect information about volunteers and also that volunteers signed a worker health statement that was not approved by the IRB. The report states that these forms have been stored separately from the field phase data. He asked for an explanation as to the purpose of the documents and why they had not been approved by the IRB. Dr. Testman responded that the initial cluster 1 was performed by an investigator who had developed his own forms and was using those for the subjects without IRB approval. This was discovered by Dr. Selim, addressed with EPA, and that investigator was removed from the study. So the forms would not be intermingled with the main study data, they were added to a confidential safe file stored separately from other study data. Dr. Philpott asked if this was reported as a deviation to the IRB. Mr. Roogow (IIRB) answered that it had been reported.

Dr. Philpott noted that a 46-year-old man reported he possessed 37 years of experience. Dr. Testman responded that there were these types of cases in the mop study as well. They are self-reported, and in one case, a subject volunteered that he had started working as a child for his parents' business.

Dr. Philpott invited Drs. Shah and Testman and Ms. Boatwright to make comments if they chose. Dr. Shaw emphasized to the HSRB that many lessons were learned from the mop study, but they could not be incorporated in the wipe study because these two studies were performed simultaneously. Many of these lessons, however, are now incorporated in the ongoing aerosol study, and lessons learned today will be incorporated into future studies, such as the upcoming study on pouring liquid.

Public Comments

Dr. Philpott invited additional public comments on the AEATF II wipe study; none were received.

Charge Questions

Ms. Sherman read the charge questions into the record:

1. Was the research reported in the AEATF II completed wipe study report faithful to the design and objectives of the protocol and governing documents of the AEATF II?
2. Has EPA adequately characterized, from a scientific perspective, the limitations on these data that should be considered when using the data in estimating exposure of those who clean indoor surfaces with antimicrobial pesticides using a trigger-spray bottle and wipes or ready-to-use wipes?
3. Does available information support a determination that the study was conducted in substantial compliance with subparts K and L of 40 CFR part 26?

Board Science Review

Dr. Green noted that this was a somewhat complicated study to review. The Agency should be commended for an extensive job in responding to the comments of the HSRB and amending their results accordingly. He also believed the Agency responded well to the limitations of the study. He answered both of the science charge questions in the affirmative.

Dr. Lebowitz complimented the Agency because he believed that the study benefited from the statistical analyses performed. Other statistical issues, such as not using the results on nonparametric bootstrapping examination, lack of sensitivity analysis to a large number of non-detects, and the differences in results between clusters, are questionable. The interpretation of the statistical results, especially the importance of slopes that were small and when the K-factor was greater than three also are questionable. He believed that inhalation is not related to AaiH, even though the Agency probably still will use the data. Further conclusions that results of the high AaiH are overestimates appear to be incorrect. High exposure results in the middle of the AaiH

range have affected the slopes too much, and it could be concluded that the response is underestimated at the high end of the AaiH. His responses to the charge questions were yes to the first charge question and no to the second charge question.

Dr. Johnson stated that he appreciated the fact that the Agency referred to geometric standard deviations and geometric means as characteristics of the data generated. He believed that the answer to both of the charge questions was yes.

Dr. Philpott commented that the discussants thought that the answer to the first charge question is "yes, the study is faithful to the design and objectives of the protocol and governing documents," but there is still some question as to whether the limitations have been characterized adequately.

Dr. Young mentioned page 35, Figure 21 in the ICF International document. This appears to have a cluster of points in the left corner and another cluster in the upper right corner. The cluster in the left corner could be an artifact of the non-detects, which are probably driving the whole regression. If this cluster is covered, the figure looks like a scatter plot. She is not sure that there is evidence of a relationship. It may be that officials examine the hands-only analysis because there are no non-detects, so that it can be discovered how much the non-detects are influencing the analysis. Mr. Leighton clarified that her recommendation would be to return to those analyses and examine the non-detects. Dr. Young stated that the hand data should be examined because there are no non-detects and then non-detects could be marked to see how much they are driving the analysis. Additionally, what is referred to as an arithmetic mean is a model-based estimate of the mean.

Dr. Popendorf stated that the target application rate was 7 mg per square meter (mg/m^2) of treated surface as noted in the protocol. The data show that few people reached that target. Subjects worked as they normally did, which is another goal; perhaps the two goals are conflicting. He did not know how that affected achieving the first charge question. Dr. Philpott commented that the way the first charge question had been interpreted by the HSRB was by asking whether there were any gross deviations from the protocol that called into question the validity of the results. Dr. Popendorf stated that in light of this interpretation, his comment did not indicate a fatal flaw. He commented that the RTU and trigger spray data are internally consistent, but he is not sure that they are applicable to the per unit AaiH concept. He further observed that the combination of predominance of the hand exposure and the design of the wash recovery study might help explain why there is less than a linear correlation between AaiH and exposure. The areas treated and the doses in the two studies were similar; the only difference is in the amount used. That difference is an artifact of the study design, and it may not be significant in and of itself but will have an impact in the way the data are used. The amount of liquid in the trigger bottles was measured, and one would assume that the amount used was applied to the surfaces, was deposited on the worker, or stayed on the rag. In the RTU case, the number of wipes used was counted. The biggest contributor to the difference was the amount of ai that stayed on the rag or wipe. The amount used is not equal between the two. With the way the amount used is calculated, the resulting unit exposures may not be very useful. Mr. Leighton noted that if a wipe with 0.04 percent ai was used, x amount of hand exposure would occur, and if a product that was 10 times more concentrated was used, it would be assumed that more ai

would be deposited on the hands. Dr. Popendorf noted that because the 7 mg/m^2 was not achieved, there might be some extrapolation.

Dr. Popendorf observed that data indicate that the trigger spray bottle users had an average of 92 percent of the total dose on their hands, and the RTU users had 98 percent. In this study, the lowest exposure time was 37 minutes, and the highest was 201 minutes. There is no information to indicate the effect of residence time. The fact that a fixed recovery factor is used for task durations that span a great deal of time means more exposure is being added to the long task performers. The dermal dose versus the duration of task is fairly linear. If dose measurements are examined as a function of task duration, they are spread out. If the rate of dose is examined, measurements show that a higher dose is seen at short duration, which would be exactly compatible with the pesticide recovery. A linear factor would predict a nonlinear correlation with Aai handling. The results are compatible with the limitation of how wash recovery is corrected for. Mr. Leighton noted that for DDAC, the dermal absorption is very low, less than 1 percent. Dr. Popendorf commented that the recovery study was not a problem, just a limitation. The implication is that there would be an exponential recovery, and the data show an exponential measure of deposition, so they are compatible.

Dr. Fernandez recommended that the raw data used in the analyses be included in the report so that the statisticians can use the data and run the analyses themselves.

Dr. Philpott stated that the consensus statement for the first charge question would be yes with the caveat that the target application rate of 7 mg/m^2 was not achieved, and although this was not a fatal flaw, it does mean that perhaps one of the objectives was not met. Dr. Shah commented that even though 7 mg/m^2 was the target, the maximum duration a subject can work was examined, and 210 minutes was the answer determined. Dr. Philpott stated that the target was something to be considered, and perhaps also in future study designs. The stated objective of amount of surface area to be covered was not achieved. Dr. Popendorf added that it could be mentioned that there was an unrecognized conflict with the other objective of letting subjects work as they normally would.

Dr. Philpott noted, with respect to the second charge question, that although there was general consensus that the Agency has characterized the limitations on the data well, the Board noted a few additional limitations to consider, mainly: the fact that the large number of non-detects seem to be causing an anchoring effect in the analysis, and it might be beneficial to examine how these non-detects are driving the statistical analysis by examining the hand exposure; the observation to be careful in the comparison between the spray and the RTU wipes because although there is confidence that the AaiH in the spray was the AaiH on the surface, for the RTU wipes, some residue would remain on the wipe, and this was not quantified; and there was concern about the recovery factor as applied to the hand-wash studies, particularly because the effect of residence time in terms of recovery was not really addressed.

Dr. Lebowitz will add in his report that the main concern about the interpretation of statistical results, and the over-reliance on small slopes raises real questions about the true relationship with the AaiH.

Dr. Green raised the point that the term "wipe study" was used for both trigger spray and wipe scenarios, which was unclear. Dr. Philpott noted that the HSRB and EPA will work to ensure that the charge questions are clearer next time.

Board Ethics Review

Dr. Northington Gamble thanked Ms. Sherman for a very comprehensive report. She commented that on page 5, in discussion of demographics, the terms English and Spanish are used, and English-speaking and Spanish-speaking should be used instead. Additionally, it is mentioned in the report that this study was discussed at the October 2010 HSRB meeting. The use of subjects who were in fair health was discussed, and in the report, it was mentioned that in the future better specificity on health status should be used. Not mentioned in this report was another issue raised at the October 2010 meeting: the fact that reports of all research that undergo expedited IRB review should be submitted to the Agency. Dr. Northington Gamble noted that earlier in the meeting she had raised the issue of lack of response to HSRB comments about the consent form and the flyer, but this did not compromise the ethical content of the research; however, a follow-up with the sponsor is highly recommended. Ms. Sherman responded that EPA provides its review to the sponsor before the Board meeting, and the documents are not seen again. She assumed it was an oversight that inhalation monitoring was not included on the flyer. Dr. Northington Gamble noted that the subject who left early because he was not feeling well was a problem. If she knew more about what happened, she would feel more comfortable stating that this study met all of the ethical standards.

Dr. Menikoff stated that he would be comfortable saying that the study was in substantial compliance with the standards. The study does not deal with experimental compounds, but one that is used by thousands every day. Appropriate medical personnel were on site, and at the worst, regarding the individual who left early, the nurse made an error in medical judgment. Information is missing on why this subject left, but that does not need to be answered to make the determination that ethical standards were met. Ms. Sherman commented that if the subject thought that he was ill as a result of participation in the study, she would hope that he would have gotten back in contact. Dr. Northington Gamble noted that it was unclear in the information logs. Dr. Philpott added that if a person came to the study and self-reported feeling ill, they should not be part of the study.

Dr. Sharpe stated that substantial compliance probably has been met, but there is no harm in seeking additional information to obtain an answer to the question or to learn that the answer cannot be determined. Dr. Philpott noted that policies and procedures were in place for medical care, and the follow-up requirement is only for those who require emergency medical care. Perhaps the sponsors should adjust the SOP slightly to follow up on anyone who feels ill.

Dr. Philpott stated that the general consensus is that overall, there was substantial compliance with subparts K and L of 40 CFR part 26, but the sponsor is encouraged to determine what happened to the individual who left early and let the Agency and the IRB know. Dr. Northington Gamble added, independent of the charge question, that there should be policies in place to address a situation in which someone comes to the study and self-reports as ill. Ms. Sherman commented that the AEATF II had good procedures in place, and it generally followed

the procedures. She agrees that there is not enough information in the log regarding the subject who left early, but she believed that the study was in substantial compliance. Dr. Philpott agreed that the Board's consensus was that the study was conducted in substantial compliance with applicable standards.

Preview of Upcoming Meetings

Ms. Sherman noted that there would be no June meeting of the HSRB. For the meeting in October, EPA expects to receive two new protocols from the AHETF and a protocol from the AEATF II on pouring liquids. A completed mosquito repellant study on No Mas repellant also may be ready for Board review because the research may be conducted this summer.

Dr. Philpott thanked the Board for their hard work and participation and turned the meeting over to Mr. Downing.

Adjournment

Mr. Downing thanked the Board for a productive meeting and noted that the next meeting would be 2 or 3 days in length and held between October 18 and 22, 2011. He adjourned the meeting at 12:45 p.m.

Respectfully submitted:

Jim Downing
Designated Federal Officer
Human Studies Review Board
United States Environmental Protection Agency

Certified to be true by:

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

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

Attachments

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

Attachment A

EPA HUMAN STUDIES REVIEW BOARD MEMBERS

Chair

*Sean Philpott, Ph.D., M.S. Bioethics — Term: 3/27/2006–10/31/2011
Director, Research Ethics
The Bioethics Program
Union Graduate College–Mt. Sinai School of Medicine
Schenectady, NY

Vice Chair

*Janice Chambers, Ph.D., D.A.B.T. — Term: 3/27/2006–10/31/2011
William L. Giles Distinguished Professor
Director, Center for Environmental Health Sciences
College of Veterinary Medicine
Mississippi State University
Mississippi State, MS

Members

*George C.J. Fernandez, Ph.D. — Term: 5/1/2010–8/31/2013
Director, Center for Research Design and Analysis
University of Nevada–Reno
Reno, NV

*Vanessa Northington Gamble, M.D., Ph.D. — Term: 10/19/2009–10/31/2012
University Professor of Medical Humanities and
Professor of History
Gelman Library
The George Washington University
Washington, DC

*Sidney Green, Jr., Ph.D., Fellow ATS — Term: 10/19/2009–10/31/2012
Department of Pharmacology
Howard University College of Medicine
Howard University
Washington, DC

*Dallas E. Johnson, Ph.D. — Term: 8/31/2007–8/31/2013
Professor Emeritus
Department of Statistics
Kansas State University
Manhattan, KS

*Michael D. Lebowitz, Ph.D., FCCP — Term: 3/27/2006–8/31/2012
Retired Professor of Public Health
(Epidemiology) & Medicine & Research Professor of Medicine
University of Arizona
Tucson, AZ

*José E. Manautou, Ph.D. — Term: 5/1/2010–8/31/2013
Associate Professor of Toxicology
Department of Pharmaceutical Sciences
School of Pharmacy
University of Connecticut
Storrs, CT

Jerry A. Menikoff, M.D. — Term: 3/27/2006–8/31/2012
Director, Office for Human Research Protections
Department of Health and Human Services
Rockville, MD

*^Rebecca T. Parkin, Ph.D., M.P.H. — Term: 10/1/2007–8/31/2013
Associate Dean for Research and Public Health Practice
School of Public Health and Health Services
The George Washington University
Washington, DC

*William J. Popendorf, Ph.D. — Term: 10/19/2009–10/31/2012
Professor
Department of Biology
Utah State University
Logan, UT

Virginia Ashby Sharpe, Ph.D. — Term: 5/1/2010–8/31/2013
National Center for Ethics in Health Care
Veterans Health Administration
Department of Veterans Affairs
Washington, DC

*Linda J. Young, Ph.D. — Term: 3/28/2008–8/31/2012
Department of Statistics
Institute of Food and Agricultural Sciences
University of Florida
Gainesville, FL

*Special Government Employee (SGE)
^Not in attendance on April 13-14, 2011

Attachment B

Federal Register Notice Announcing Meeting

[Federal Register Volume 76, Number 59 (Monday, March 28, 2011)]
[Notices]
[Pages 17121-17123]
From the Federal Register Online via the Government Printing Office [www.gpo.gov]
[FR Doc No: 2011-7198]

ENVIRONMENTAL PROTECTION AGENCY

[EPA-HQ-ORD-2011-0124; FRL-9287-1]

Human Studies Review Board (HSRB); Notification of a Public Meeting

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

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

DATES: This public meeting will be held on April 13-14, 2011, from approximately 8:30 a.m. to approximately 5 p.m. Eastern Time.

ADDRESSES: Submit your written comments, identified by Docket ID No. EPA-HQ-ORD-2011-0124, 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 Avenue 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 Avenue NW., Washington, DC 20460. The hours of operation are 8:30 a.m. to 4:30 p.m. Eastern Time, Monday through Friday, excluding Federal holidays. Please call (202) 566-1744 or e-mail the ORD Docket at ord.docket@epa.gov for instructions. Updates to Public Reading Room access are available on the Web site (http://www.epa.gov/epahome/dockets.htm).

Instructions: Direct your comments to Docket ID No. EPA-HQ-ORD-2011-0124. 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 the disclosure of which 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

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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.

FOR FURTHER INFORMATION CONTACT: Any member of the public who wishes to receive further information should contact Jim Downing at telephone number: (202) 564-2468; fax: (202) 564-2070; e-mail address: downing.jim@epa.gov, or Lu-Ann Kleibacker at telephone number: (202) 564-7189; fax: 202-564-2070; e-mail address: kleibacker.lu-ann@epa.gov; mailing address: Environmental Protection Agency, Office of the Science Advisor (8105R), 1200 Pennsylvania Avenue NW., Washington, DC 20460. General information concerning the EPA HSRB can be found on the EPA Web site at http://www.epa.gov/osa/hsrb/.

SUPPLEMENTARY INFORMATION:

Location: Holiday Inn National Airport, 2650 Jefferson Davis Highway, 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 persons listed under FOR FURTHER INFORMATION CONTACT at least ten business days prior to the meeting using the information under FOR FURTHER INFORMATION CONTACT, so that appropriate arrangements can be made.

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 section I. "Public Meeting," under subsection D. "How May I Participate in this Meeting?" of this notice.

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 particular 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 Jim Downing or Lu-Ann Kleibacker listed under FOR FURTHER INFORMATION CONTACT.

B. How can I access electronic copies of this document and other related information?

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

Docket: All documents in the docket are listed in the http://www.regulations.gov index. Although listed in the index, some information is not publicly available, e.g., CBI or other information whose disclosure is restricted by statute. Certain other material, such as copyrighted material, will be publicly available only in hard copy. Publicly available docket materials are available either electronically in http://www.regulations.gov or in hard copy at the ORD Docket, EPA/DC, Public Reading Room. The EPA/DC Public Reading Room is located in the EPA Headquarters Library, Room Number 3334 in the EPA West Building, located at 1301 Constitution Avenue NW., Washington, DC 20460. The hours of operation are 8:30 a.m. to 4:30 p.m. Eastern Time, Monday through Friday, excluding Federal holidays. Please call (202) 566-1744 or e-mail the ORD Docket at ord.docket@epa.gov for instructions. Updates to Public Reading Room access are available on the Web site (http://www.epa.gov/epahome/dockets.htm). EPA's position paper(s), charge/questions to the HSRB, and the meeting agenda will be available by the end of March 2011. 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 Building, located at 1301 Constitution Avenue NW., Washington, DC 20460. The hours of operation are 8:30 a.m. to 4:30 p.m. Eastern Time, Monday through Friday, excluding Federal holidays. Please call (202) 566-1744 or e-mail the ORD Docket at ord.docket@epa.gov for instructions. Updates to Public Reading Room access are available on the Web site (http://www.epa.gov/epahome/dockets.htm). EPA's position paper(s), charge/questions to the HSRB, and the meeting agenda will be available by the end of March 2011. In addition, the Agency may provide additional background documents as the materials become available. You may obtain electronic copies of these documents, and certain other related documents that might be available electronically, from the regulations.gov Web site and the EPA HSRB Web site at http://www.epa.gov/osa/hsrb/. For questions on document availability, or if you do not have access to the Internet, consult either Jim Downing or Lu-Ann Kleibacker 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:

1. Explain your views as clearly as possible.
2. Describe any assumptions that you used.
3. Provide copies of any technical information and/or data that you used to support your views.

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

5. 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-2011-0124 in the subject line on the first page of your request.

1. Oral comments. Requests to present oral comments will be accepted up to Wednesday, April 6, 2011. 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 Jim Downing or Lu-Ann Kleibacker, under FOR FURTHER INFORMATION CONTACT, no later than noon, Eastern Time, Wednesday, April 6, 2011, in order to be included on the meeting agenda and to provide sufficient time for the HSRB Chair and HSRB Designated Federal Official (DFO) to review the meeting agenda to provide an appropriate public comment period. The request should identify the name of the individual making the presentation and the organization (if any) the individual will represent. Oral comments before the HSRB are generally limited to five minutes per individual or organization. Please note that this includes 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 the time limitations by having numerous individuals sign up separately to speak on their behalf. If additional time is available, further public comments may be possible.

2. Written comments. Submit your written comments prior to the meeting. 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 this meeting. If you submit

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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, Wednesday, April 6, 2011. You should submit your comments using the instructions in section I., under subsection C., “What Should I Consider as I Prepare My Comments for EPA?” In addition, the Agency also requests that persons submitting comments directly to the docket also provide a copy of their comments to Jim Downing or Lu-Ann Kleibacker listed under FOR FURTHER INFORMATION CONTACT. There is no limit on the length of written comments for consideration by the HSRB.

E. Background

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

1. Topics for discussion. At its meeting on April 13 and 14, 2011, EPA's Human Studies Review Board will consider scientific and ethical issues surrounding these topics:

a. The report of a completed scenario monograph and study reports from the Agricultural Handler Exposure Task Force (AHETF) measuring the dermal and inhalation exposure of professional agricultural workers applying liquid spray pesticides to tree or trellis crops using open cab airblast equipment.

b. The report of a completed scenario monograph and study report from the Antimicrobial Exposure Assessment Task Force II (AEATF II) in which the dermal and inhalation exposure of professional janitorial workers was monitored as they applied a liquid antimicrobial product to indoor surfaces using a trigger spray bottle and wipes or ready-to-use wipes.

c. A published report by Gulson et al (2010) of an intentional exposure human study measuring dermal absorption of zinc oxides contained in sunscreen.

d. A reevaluation of an intentional human dosing study with chlorpyrifos (Kisicki) previously reviewed by the HSRB; pertinent new information from the sponsor has been made available.

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

Dated: March 23, 2011.
Paul T. Anastas,
EPA Science Advisor.
[FR Doc. 2011-7198 Filed 3-25-11; 8:45 am]
BILLING CODE 6560-50-P

Attachment C

U.S. ENVIRONMENTAL PROTECTION AGENCY
HUMAN STUDIES REVIEW BOARD
APRIL 2011 PUBLIC MEETING AGENDA

Holiday Inn National Airport
2650 Jefferson Davis Highway
Arlington, VA 22202

HSRB WEB SITE: http://www.epa.gov/osa/hsrb/
Docket Telephone: (202) 566-1752
Docket Number: EPA-HQ-ORD-2011-0124

Wednesday, April 13, 2011

9:00 AM* Convene Public Meeting and Review Administrative Procedures – Mr. Jim Downing (Designated Federal Officer [DFO], Human Studies Review Board [HSRB], Office of the Science Advisor [OSA], EPA)
Introduction and Identification of Board Members – Sean Philpott, Ph.D. (HSRB Chair)
Welcome – Warren Lux, M.D. (Director of the Program in Human Research Ethics, OSA, EPA)
Opening Remarks – Steven Bradbury, Ph.D. (Director, Office of Pesticide Programs (OPP), Office of Chemical Safety and Pollution Prevention, EPA)
Office of Pesticide Programs Follow-up on Previous HSRB Recommendations – Ms. Kelly Sherman (OPP, EPA)

Session 1: Completed AHETF research on exposure of workers applying pesticide sprays using open-cab airblast equipment

9:30 AM EPA Science and Ethics Reviews – Mr. Matthew Crowley (OPP, EPA) and Ms. Kelly Sherman (OPP, EPA)
10:30 AM Board Questions of Clarification – Sean Philpott, Ph.D. (HSRB Chair)
11:00 AM Public Comments
11:15 AM Break
11:30 AM Board Discussion – Science

Charge to the Board:

- Was the research reported in the Agricultural Handler Exposure Task Force (AHETF) completed monograph report and associated field study reports faithful to the design and objectives of the protocol, SOPs, and governing documents?
- Has EPA adequately characterized, from a scientific perspective, the limitations on these data that should be considered when using the data in estimating exposure of those who apply pesticides with open cab airblast equipment?

12:15 PM Board Discussion – Ethics

Charge to the Board:

- Does available information support a determination that the studies were conducted in substantial compliance with subparts K and L of 40 CFR part 26?

12:45 PM Lunch

Session 2: A published report (Gulson et al. 2010) of an intentional exposure human study measuring dermal absorption of zinc oxides contained in sunscreens

1:30 PM EPA Science and Ethics Reviews – Jessica Ryman, Ph.D. (OPP, EPA) and Ms. Laura Parsons (OPP, EPA)
2:15 PM Board Questions of Clarification – Sean Philpott, Ph.D. (HSRB Chair)
2:45 PM Public Comments
3:00 PM Board Discussion – Science

Charge to the Board:

- Is the Gulson et al. (2010) study scientifically sound, providing reliable data?
- If so, is the Gulson et al. (2010) study relevant for qualitative use in support of an assessment of the absorption of zinc oxide through the skin?

3:45 PM Break

4:00 PM Board Discussion – Ethics

Charge to the Board:

- Is there adequate information to determine that the Gulson et al. (2010) study was conducted in substantial compliance with procedures at least as protective as those in subparts A - L of EPA's regulation at 40 CFR part 26?

Session 3: Reconsideration of two concerns previously raised by the HSRB in its June 2009 review of an intentional human dosing study with chlorpyrifos (Kisicki et al., 1999); additional pertinent information was made available by the sponsor related to these two concerns

4:30 PM Introduction of Topic – Sean Philpott, Ph.D. (HSRB Chair)
4:45 PM Board Discussion – Science

Issues for Discussion:

- Do the recommendations provided by the HSRB at its June 2009 meeting and in its subsequent report regarding the reliability of data on the urinary metabolite trichloropyridinol in the Kisicki et al. (1999) study change in light of the new information provided?

- Do the recommendations provided by the HSRB at its June 2009 meeting and in its subsequent report regarding the level of absorption of chlorpyrifos in the Kisicki et al. (1999) study change in light of the new information provided?

5:30 PM Adjournment

U.S. ENVIRONMENTAL PROTECTION AGENCY
HUMAN STUDIES REVIEW BOARD
APRIL 2011 PUBLIC MEETING AGENDA

Holiday Inn National Airport
2650 Jefferson Davis Highway
Arlington, VA 22202

HSRB WEB SITE: http://www.epa.gov/osa/hsrb/
Docket Telephone: (202) 566-1752
Docket Number: EPA-HQ-ORD-2011-0124

Thursday, April 14, 2011

10:00 AM* Convene Public Meeting – Mr. Jim Downing (DFO, HSRB, OSA, EPA)
Introduction and Identification of Members – Sean Philpott, Ph.D. (HSRB Chair)
Follow-up from Previous Day – Ms. Kelly Sherman (OPP, EPA)

Session 1: Completed AEATF II research on exposure of professional janitorial workers when wiping indoor surfaces with an antimicrobial pesticide

10:15 AM EPA Science and Ethics Reviews – Mr. Timothy Leighton (OPP, EPA) and Ms. Kelly Sherman (OPP, EPA)
11:00 AM Board Questions of Clarification – Sean Philpott, Ph.D. (HSRB Chair), EPA, Principal Investigator/Sponsor
11:30 AM Public Comments
11:45 AM Board Discussion – Science

Charge to the Board:

- Was the research reported in the Antimicrobial Exposure Assessment Task Force II (AEATF II) completed wipe study report faithful to the design and objectives of the protocol and governing documents of AEATF II?
- Has EPA adequately characterized, from a scientific perspective, the limitations on these data that should be considered when using the data in estimating exposure of those who clean indoor surfaces with antimicrobial pesticides using a trigger-bottle and wipes or ready-wipes?

12:30 PM Board Discussion – Ethics

Charge to the Board:

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

1:00 PM Preview of Upcoming Meetings – Ms. Kelly Sherman (OPP, EPA)

1:10 PM Adjournment