Minutes of the
United States Environmental Protection Agency (EPA)
Human Studies Review Board (HSRB)
July 12 – 13, 2016, Public Meeting
HSRB Website: www.epa.gov/osa/human-studies-review-board

Committee Members:	(See EPA HSRB Members List—Attachment A)	
Date and Time:	Tuesday, July 12, 2016, 1:00–5:15 p.m. EDT Wednesday, July 13, 2016, 1:00–4:45 p.m. EDT (See *Federal Register* Notice—Attachment B)	
Location:	Via Teleconference and Webinar	
Purpose:	The EPA HSRB provides advice, information and recommendations on issues related to the scientific and ethical aspects of human subjects research.	
Attendees:	Chair:	Liza Dawson, Ph.D.
	Vice Chair:	Edward Gbur, Jr., Ph.D.
	Board Members:	Gary L. Chadwick, Pharm.D., M.P.H, C.I.P. Kyle L. Galbraith, Ph.D. Jewell H. Halanych, M.D., M.Sc. Randy Maddalena, Ph.D. Kenneth Ramos, M.D., Ph.D., Pharm.B. Suzanne M. Rivera, Ph.D., M.S.W. (July 13 only) Helen H. Suh, Ph.D. Jun Zhu, Ph.D.
Meeting Summary:	Meeting discussions generally followed the issues and timing as presented in the Meeting Agenda (see Attachment C), unless noted otherwise.	

Tuesday, July 12, 2016

Convene Public Meeting

Mr. Jim Downing, Designated Federal Officer (DFO), HSRB (or Board), Office of the Science Advisor, EPA (or Agency), convened the meeting at 1:00 p.m. and welcomed Board members, EPA colleagues and members of the public. Mr. Downing expressed the Agency's appreciation to the Board members for their time and efforts preparing for the meeting, and he also thanked his EPA Office of Pesticide Programs (OPP) colleagues for their efforts in preparing for the meeting.

Mr. Downing noted that in his role as DFO under the Federal Advisory Committee Act (FACA), he serves as liaison between the HSRB and EPA and is responsible for ensuring that all FACA provisions are met regarding the operations of the HSRB. Also in his role as DFO, he works with appropriate Agency officials to ensure that all appropriate ethics regulations are satisfied. HSRB members were briefed on provisions of the federal ethics and conflict-of-interest laws and have completed government financial disclosure reports, which have been reviewed to ensure that all ethics requirements are met.

Mr. Downing informed Board members that two interesting topics would be discussed during the meeting. Supporting documents for the meeting are available on the HSRB website.[1] He noted that agenda times are approximate and that adequate time will be allowed for Agency presentations, public comments and the Board's deliberations.

Following EPA presentations, time has been allocated for the Board to ask clarifying questions. Time also has been allocated for public comment. Mr. Downing noted that no individuals had provided comments in advance of the meeting, and he had received no requests to provide public comments during the meeting. The Chair will call for public comments during the public comment period. Such comments should be limited to 5 minutes.

In accordance with FACA requirements, 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 calendar days. The approved minutes will be available on the HSRB website. The HSRB also will prepare a final report in response to the charge questions posed by the Agency, which will include the Board's review and analysis of materials presented and the Board's advice and recommendations to the Agency. The final report will be available on the HSRB website.

Virtual Meeting Operations

Mr. Downing and Dr. Liza Dawson, HSRB Chair, reviewed guidelines for virtual participation in the meeting. Mr. Downing indicated that the chat feature of Adobe Connect would not be used, the hand-raising feature should be used by Board members to request to speak, and the approval/disapproval feature should be used by Board members for voting. Dr. Dawson reminded participants that their telephone lines should be muted when they are not speaking. When speaking, participants should identify themselves for accurate recordkeeping in the meeting minutes.

Introduction of Board Members

Mr. Downing conducted a roll call of the Board members. Dr. Dawson then welcomed the Board members and asked them to introduce themselves, providing their names, affiliations and areas of expertise. The Board members, including Dr. Edward Gbur, Jr., HSRB Vice-Chair, completed their introductions.

Opening Remarks

On behalf of EPA, Dr. Toby Schonfeld, EPA Human Subjects Research Review Official, welcomed the participants. She anticipated a productive 2-day meeting discussing two important topics. Dr. Schonfeld expressed her appreciation for the work of the Board members and OPP representatives in preparing for the meeting.

Brief Update on Research Discussed at Last HSRB Meeting

Ms. Maureen Lydon, OPP, updated the Board members on the two topics discussed during its January 2016 meeting. In January, OPP and the HSRB discussed the Davis et al research article on

[1] The HSRB website is available at www.epa.gov/osa/human-studies-review-board.

tetrachlorvinphos (TCVP) published in 2008. After the last meeting, as required by the federal rule on protecting human subjects, EPA published a notice of intent to take into account the Davis research in EPA's risk assessment and provided the opportunity for public comment. Four comments were received during the comment period which closed May 11, 2016. The Agency considered the HSRB's and public comments on the use of the data and are currently working on the TCVP risk assessment. EPA expects to publish the final TCVP risk assessment by the end of the 2016 calendar year.

Dr. Dawson asked whether the TCVP risk assessment will lead to a consumer advisory or other action by the Agency. Ms. Lydon responded that EPA's current goal is to finalize the risk assessment. After considering the results of the risk assessment, the Agency will determine next steps.

Ms. Lydon stated that also in January 2016, the Board discussed five completed studies for field testing of S.C. Johnson mosquito repellent products to support their use of the EPA repellency awareness graphic. Each study proposed the approximate complete protection time or CPT that would be included on an EPA repellency awareness graphic on each of the five product labels. The graphic communicates the product's duration of repellent efficacy against mosquitoes and/or ticks. In March 2016, OPP's registration division received applications from S.C. Johnson to amend the labels of the five products to include the repellency awareness graphic. As part of this process, OPP reviews the entire proposed label for each product, not just the repellency awareness graphic. The Agency currently is conducting its label reviews, which includes interaction with the registrant.

Completed Studies and Monograph Report for Agricultural Handler Exposure During Open Pour Mixing/Loading of Wettable Powders (Agricultural Handlers Exposure Task Force)

Ms. Lydon provided background on EPA's request for HSRB's review of the above completed studies and monograph report. The scenario monograph report on agricultural handler exposure from open pour mixing/loading of wettable powders summarizes the results of two studies: AHE39, which was initiated prior to the effective date of the rule on protecting human subjects (April 7, 2006), and study AHE80, which was initiated after the effective date of the final rule.

Under 40 CFR Section 26.1604, EPA is required to seek input from the HSRB for human studies covered by EPA's human studies rule that are initiated after April 7, 2006. For human studies initiated prior to that date, EPA is not required to consult with the HSRB unless the study was conducted to identify or measure a toxic effect. Because exposure study AHE39 was initiated prior to the effective date of the human studies rule, Ms. Lydon clarified that at this HSRB meeting, EPA is seeking HSRB feedback only on study AHE80, as required by EPA's human studies rule.

<u>EPA Science Review Highlights</u>

Mr. Matt Crowley, OPP, provided a science review of the Agricultural Handlers Exposure Task Force's (AHETF or Task Force) pesticide handler exposure study of mixing/loading of pesticide products formulated as wettable powders. The scenario is defined as pouring wettable powder pesticides directly into a spray application equipment tank water or into slurry or premix tank water and then transferring the spray mixture to the application equipment. The overall study objective was to capture the variability of expected dermal and inhalation exposures for workers who are mixing and loading pesticides formulated as wettable powders. The primary quantitative data analysis benchmark related to the accuracy of exposure estimates and the secondary quantitative data analysis benchmark was the ability to distinguish proportionality between dermal exposure and the amount of active ingredient handled (AaiH). These objectives guided study design regarding the number, timing and location of monitoring units.

The general study design was documented in the 2010 AHETF Governing Document and used a clustered sampling approach to satisfy study objectives while minimizing costs and number of participants. The HSRB approved the protocol for AHE80 in 2011, which proposed a 5 × 4 sampling configuration (i.e., four clusters of five participants each) supplemented by the data from AHE39, which consisted of one cluster of five workers. Such factors as location and employer were to be diversified to obtain the desired exposure variability, with randomness incorporated into the recruitment process to mitigate potential selection bias. Dermal (i.e., hands, head and body) and inhalation exposure were to be monitored using hand washes, face/neck wipes, whole-body dosimeters in six parts, and a glass fiber filter attached to an air pump. Mr. Crowley presented data on the limits of detection (LODs) and limits of quantitation (LOQs) of the AHE80 exposure monitoring methods, measured in µg sulfur per sample (AHE39 monitored exposure to diazinon, a nonsulfur pesticide). The few monitoring results that registered below the LODs or LOQs were samples from the glass fiber filter back sections, which measure breakthrough, and approximately one-third of the hand wash samples.

Mr. Crowley discussed protocol amendments and deviations. The AHE80 protocol was amended to aid in finding study participants and adjust levels of positive controls to match observed monitoring results. EPA found these amendments to be reasonable. AHE80 protocol deviations included field fortification samples conducted at levels different than protocol; failure of one worker to wear label-required eye protection during first tank load; failure to collect hand wash samples at some smoking breaks; and failure to wash hands after contacting product without gloves, which will be discussed further in EPA's ethics review of AHE80. Mr. Crowley stated that EPA reviewers do not believe that the deviations do not significantly undermine or compromise the exposure results.

Quality assurance and quality control practices were adhered to. Quality assurance procedures ensured that the study followed EPA's Good Laboratory Practice Standards, including training research personnel, performing protocol and amendment review, and including signed quality assurance statements in the study report. Negative (i.e., laboratory or field blanks) and positive (i.e., laboratory spikes or field fortifications samples) control samples were collected. Some blanks had detectable results, but no systematic correlation with monitoring results was found, and no corrections were made for blanks. Laboratory recoveries were close to 100 percent, and average field fortification recoveries ranged from 27 to 123 percent. . In some instances, calculation of average field fortification recoveries excluded unusual results. Monitoring results were adjusted to account for field fortification sample recoveries that differed from 100 percent, with a maximum adjustment factor of 1.2. Plotting the coefficient of variation versus the mean for field fortification triplicates reveals that almost all results showed acceptable recovery (70–120%) and variability (< 25% coefficient of variation).

Mr. Crowley described scenario characteristics. The scenario activity involved filling a tank (or intermediate holding tank or bucket) partially with water, opening the bag or box, measuring the required amount (if necessary), pouring the wettable powders into the tank or an intermediate tank, transferring the mixture to pesticide application equipment if mixed in an intermediate tank, and adding water as necessary to achieve the desired concentration. The sampling locations and dates for AHE80 were expanded geographically and temporally to account for recruitment challenges, resulting in nine clusters using a 90-day threshold or 15 subclusters using a 5-day threshold. Sampling took place in 2006 for AHE39 and from 2011 through 2013 for AHE80. Sampling occurred in Idaho (one subcluster), Michigan (four subclusters), New York (two subclusters), Florida (five subclusters) and California (three subclusters). The workers were all male, which is characteristic of the mixing/loading workforce as a whole, and the workers were variable in age, work experience, weight and employment status. In one instance, a malfunctioning water source prevented a worker in Michigan from mixing the spray. As a result, 24 workers were monitored instead of 25. The study's goal was to monitor multiple types of mixing and loading, but most of the mixing occurred directly in the application tank (16 workers), which was not a protocol deviation because monitoring the three mixing/loading methods equally was not

specified in the protocol. The other mixing/loading types were premixing in a slurry bucket (five workers), premixing in a holding tank (one worker) and using on-board inductors (two workers). The amount mixed and loaded—as measured by number of tank loads, gallons of solution prepared and time—was diverse, but none of the workers were handling low levels of of AaiH, which was attributed to typical working conditions for the scenario.

Exposure monitoring results were calculated for hand dermal exposure (sum of one to four samples per monitoring unit), head dermal exposure (extrapolated from the sampled area to the whole head), body dermal exposure (sum of six whole-body dosimeter sections), and inhalation exposure (the sum of the front and back filter sections, adjusted by the breathing and pump rate), adjusting for average recovery of the corresponding field fortification matrix and level. Each worker's total dermal and inhalation exposures then were divided by the amount of active ingredient he handled. As discussed at the June 2007 HSRB meeting, dermal exposure is method efficiency-adjusted (MEA) upward by a factor of two when dermal exposure represents 20 to 60 percent of total exposure, an approach contested by the Task Force in a recent submission that EPA is reviewing. For this scenario, however, the dermal exposure results averaged less than 20 percent of the total; therefore, the hand wash and face/neck wipe data do not reflect a twofold MEA adjustment. The results for dermal exposure averaged 48.1 micrograms per pound active ingredient (µg/lb ai) (range = 0.64–237 µg/lb ai, 95th percentile [P95] = 129 µg/lb ai). Inhalation exposure monitoring results ranged from 0.031 to 13.5 µg/lb ai (average = 2.36 µg/lb ai, P95 = 9.39 µg/lb ai).

The exposure monitoring results—normalized to the amount of AaiH (i.e., unit exposure)—were analyzed by three methods: empirical estimates (i.e., simple statistics), simple random sample (i.e., a log-normal distribution of data that were assumed to be independent), and mixed model (i.e., a log-normal distribution that incorporates potential correlation of data within clusters). The different assumptions of each approach result in differing amounts of uncertainty. A log-normal distribution of the exposure monitoring results was assumed and, when plotted, the dermal and inhalation unit exposure monitoring results were consistent with a log-normal, rather than a normal distribution. Unit dermal and inhalation exposure data plotted versus cluster number, which describes spatial and temporal proximity, illustrated that the AHETF analysis properly accounted for cluster effects, which are quantified by the intra-class correlation (ICC). EPA agreed with the Task Force that considering the data structure, a log-normal mixed model is most appropriate for statistical analysis. Confidence intervals (CIs) were determined using bootstrap simulations. The geometric standard deviation unit exposures were 3.42 µg/lb ai (95% CI = 2.39–5.16 µg/lb ai) and 6.58 µg/lb ai (95% CI = 3.35–13.37 µg/lb ai) for dermal and inhalation exposure, respectively, with ICCs of 0.00 µg/lb ai for both dermal and inhalation exposure.

The primary study objective, meeting the accuracy benchmark of threefold relative accuracy, was met for dermal exposure, but inhalation exposure showed higher variability. The secondary study objective is used to assess whether the study has sufficient statistical power to distinguish independence from proportionality between dermal exposure and the amount of AaiH, and EPA agrees that meeting this objective is of lessor importance. A regression slope of 1 indicates proportionality, whereas a slope of 0 indicates independence, and a width of 95 percent CI of 1.4 or less is consistent with meeting the study design objective of 80 percent statistical power. The slopes of the unit dermal and inhalation exposure regression analysis were closer to 1 than 0, but the CIs were wide for both the dermal (95% CI width = 1.5) and inhalation (95% CI width = 1.66) monitoring results, and the confidence interval of the slopes include both 0 and 1 for the dermal exposure route. Mr. Crowley noted that the unit dermal and inhalation exposures for M13, who had the highest AaiH, were very different from the others, and if his results are excluded, the 95th CI range of the dermal exposure route slope excludes 0.

Regarding regulatory exposure assessments, the use of the data assumes compliance with product labels (reflecting the maxim, "the label is the law"). EPA found that the study records demonstrate

compliance with product labels and the variability of expected exposure when wettable powder pesticides are used. The data would be used in the regulatory review process for new and current chemicals to quantify exposure during mixing/loading of pesticides formulated as wettable powders, which would be compared to the relevant chemical-specific toxicity benchmarks.

Mr. Crowley concluded that EPA determined that the study design was acceptable, monitoring methods were representative of the state of the science, the analysis of primary and secondary objectives was acceptable, and the data are recommended for use in regulatory assessment with AaiH normalization.

Board Questions of Clarification—Science

Dr. Gbur observed that AHE80 emphasized dermal exposure more than inhalation exposure and asked why the two exposure routes had not been considered more equally. Mr. Crowley replied that the main reason was that inhalation exposures generally are lower under the study scenario. Because the dermal route generally is the main source of exposure, the study focused on that route. Dr. Dawson asked whether the protocol prespecified an emphasis on the dermal route. Mr. Crowley responded that the dermal route was emphasized in the Governing Document and in the specific scenario design documents and protocols. Dr. Gbur noted that dermal exposure is easier to observe than inhalation exposure, which affects the throat and lungs. Mr. Crowley concurred, but assured the Board members that inhalation exposure effects will be considered in the risk assessment.

Dr. Randy Maddalena, HSRB member, noted that on slide 37, EPA indicated that the Agency was satisfied that the diversity of conditions had been adequately captured by the study, but in the EPA Science Review, the Agency had commented on study diversity limitations, including that the study considered a limited number of mixing types, and the range of active ingredient amounts handled was not optimal. Mr. Crowley replied that considering recruitment issues, the Agency had concluded that the study had captured the diversity of worker conditions as well as possible.

Dr. Gbur asked whether the "UE" value in the formula on slide 36 would be the 95th percentile value from the AHETF dataset. Mr. Crowley responded that most EPA risk assessments use the arithmetic mean, which for AHE80 was determined using the mixed model.

Dr. Gbur asked about corrections to the data for field fortification sample recoveries. Mr. Crowley explained that exposure data had been adjusted up or down according to the results of the corresponding field fortification samples, although 120 percent is the upper bound of such adjustments (i.e., raw exposure results are divided by a maximum factor of 1.2).

EPA Ethics Review Highlights

Ms. Lydon presented highlights from EPA's ethics review of study AHE80. The HSRB reviewed the draft AHE80 protocol at the January 26, 2011, HSRB meeting. Attachment 4 to EPA's ethics review summarizes the AHETF's actions to address the HSRB's comments.

Ms. Lydon presented examples of the changes made in response to the comments. First, standard operating procedure (SOP) document SOP-11-B.5 was updated so that research staff will not influence, or ask about, the personal protective equipment (PPE) that subjects normally wear in a manner that would influence the worker to wear less PPE than normal. This relates to the eligibility criterion, which states "that subjects must … usually wear the PPE listed on the label of the pesticide products that they will mix and load, and must confirm that they would not normally wear personal protective items not required by the label, on the day of the study." The consent form for AHE80 was revised to state that subjects may refuse treatment unless the medical professional decides that the subject is too ill to make a decision about getting treatment. SOP 11.H.4 on emergency procedures was updated to include the pertinent criteria for

making this decision. SOP 11.J was revised to explain how subjects will be presented with individual exposure information. Regarding Spanish translations, the AHETF consulted with bilingual trainers throughout the United States to ensure no difficulties with Spanish translations existed as a result of different dialects. The AHETF undertook a translation review project to ensure that Spanish translations were accurate. The AHETF identified bilingual pesticide safety trainers in different regions of the country. The AHETF sent the bilingual trainers both English and Spanish versions of the consent form, recruitment flyer, California bill of rights (for the California reviewers) and other support documents and asked whether they had any edits regarding the Spanish translations. They also sent a list of agricultural terms in English likely to be used in protocols at the time and asked for their translations of those terms based on the region in which they lived. Six individuals from different regions of the country reviewed the documents and provided feedback, and the AHETF incorporated this feedback. The AHETF hired a Spanish-fluent senior scientist who took into account the results of the translation review project. She translates into Spanish all consent forms and other materials. The AHETF submits her work to the overseeing institutional review board (IRB), which requests that a certified translator review, comment on, and certify the translation with a letter of accuracy. The Spanish translation follows the approved English version. The consent form was clarified regarding timing associated with pregnancy testing and what occurs if the start of the study is delayed. The SOP and support documents now clarify that a worker who identifies himself as a nonreader will select his own witness. In both the consent form and protocol, the risk of exposure to surrogate chemicals was added as a risk associated with participation in the study. The study sponsor clarified the phrase "greater than minimal risk" in the protocol so that it reads, "the likelihood of harm or discomfort is greater than what is encountered in ordinary daily life. In particular, the risk of heat-related illness (resulting from wearing an extra layer of clothing to trap chemical) will be increased due to study participation."

Regarding recruitment, some of the monitoring regions for AHE80 overlapped with study AHE120 on water-soluble packets. Many employers used both wettable powders and water-soluble packets. As a result, Protocol Amendment 4 allowed simultaneous recruitment for AHE80 and AHE120. For efficiency's sake, the Universe, Master and Qualified Recruitment Lists for the two studies were combined. A three-phase process for recruitment was described in great detail in study AHE80. EPA's ethics review includes several pages on recruitment. In summary, Recruitment Phase 1 ultimately resulted in a list of employers qualified to participate in the study. This is the Qualified Employer List referenced in the study. Recruitment Phase 2 resulted in the list of potentially eligible employers, and Phase 3 resulted in the list of eligible employers. The study provides a detailed description of the recruitment process as the study sponsor begins with the number of employers on the Universe List and ultimately arrives at the number of workers participating in the study. For example, the summary of recruitment details for Florida on Page 31 of the study gives the progression beginning with the 12,152 employers on the Universe List and ultimately arriving at five workers identified for participation in the study. After the recruitment, the Study Director scheduled and conducted the informed consent sessions and monitored workers. All growers signed the employer noncoercion statement before recruitment. EPA's ethics review compared the recruitment approach used in AHE80 with the process identified in the protocol and SOPs. EPA found that the AHETF generally followed the recruitment outlined in the protocol and SOPs with amendments approved by the overseeing IRB.

Participating subjects completed the informed consent process and signed consent forms. Consent occurred after recruitment and prior to monitoring. The Study Director met privately with each subject, reviewed the consent form section by section, and asked standard comprehension questions to document each subject's understanding. In Florida, one worker opted to have a Spanish-speaking researcher present during the consent meeting. Subjects received copies of their signed consent forms. Each subject was informed of the pesticide active ingredient and end-use product before signing the informed consent form. Consistent with the consent form and/or protocol, the AHETF reviewed the following information with subjects: how much of the product the subject might handle during the study, the required clothing and

PPE, the importance of washing hands before eating or smoking, other safety precautions that should be followed, specific risks associated with the end-use product as discussed on the label, and procedures to be followed before the start of the study and on the day of the study. All participating subjects signed the IRB-approved consent forms, which included the eligibility criteria written in plain English. AHE80 subjects wore required PPE as specified on product labeling and in the protocol, as well as outer clothing prescribed in the protocol. A medical professional was present for the duration of each monitoring event and periodically checked subjects for heat-related illness. Attachment 9 to EPA's ethics review identifies the medical professional assigned to monitor each subject. The subjects received compensation consistent with the protocol and informed consent form. This was $20 for participating in the consent meeting and $80 for each day participating in the study.

The 19 monitored workers were males between 18 and 73 years of age. One worker self-reported an age of 71, but the eligibility form, which was based on identification, reported an age of 73. No female subjects volunteered to participate in the study. No changes were made to the recruitment process to exclude female subjects. The Study Director has been conducting mixer/loader and applicator exposure studies in production agriculture since 1982 and has never encountered a female mixer/loader or applicator. The Study Director's field experience is that women are more likely to be encountered in harvesting work and agricultural reentry activities; those activities take place when workers enter fields after the fields have been treated with a pesticide, such as when hand-harvesting crops. Work experience ranged from 1 to 44 years.

Regarding eligibility criteria, one criterion in the SOP reads that the subject must "be trained in safe pesticide handling procedures in accordance with the Worker Protection Standard (WPS) or equivalent Canadian regulations, or be exempt from such training." The WPS criterion appears on the consent form as, "Confirm that you have been trained in pesticide safety or that you are not required to take this training." In EPA's ethics review, EPA asked the study sponsor to update the consent form for remaining studies, beginning in August 2016, so that it reads: "Be trained in safe pesticide handling procedures in accordance with the Worker Protection Standard (WPS), or be a certified applicator of restricted use pesticides or a certified crop advisor." EPA recommends a slight change to this language. The WPS includes three exemptions for not completing WPS training: (1) being a certified applicator of restricted use pesticides; (2) being a certified crop advisor; or (3) owning an agricultural establishment or being an immediate family member of the owner. These three exemptions are why the criterion in the SOP refers to being trained in accordance with the WPS or being exempt. To reflect all three exemptions, EPA wants to further simplify the language proposed for the consent form. EPA recommends the consent form read as follows: "Confirm that you have been trained in how to handle pesticides safely as described in the Worker Protection Standard (WPS) or that you are not required to take this training."

When reviewing the consent form section by section with subjects, when the AHETF discusses this criterion, EPA recommends that the AHETF ask each potential subject at least the following four comprehension questions: (1) Have you completed Worker Protection Standard training for handlers? (2) Do you own an agricultural establishment? Are you a member of the immediate family of the owner? (3) Are you a certified applicator of restricted use pesticides? (4) Are you a certified crop advisor? As described in the WPS, positive responses to questions 2, 3 or 4 exempt the subject from WPS training. EPA also recommends that if the AHETF study does not begin on the same day as the consent process and if the subject is exempt from WPS training, the AHETF should email to the subject a link to WPS training information. The study sponsor should do this only if the subject affirms that he or she is interested in receiving this information. Per the WPS rule, the subject will not be required to look at the training information, but the material will be provided as a reference for participating subjects. This is another way to promote safe handling of pesticides. In summary, the WPS criterion on the consent form currently reads: "Confirm that you have been trained in pesticide safety or that you are not required to take this training." EPA recommends that the study sponsor change this for the remaining studies to

specifically reference the WPS, beginning in August 2016. The updated consent form would read: "Confirm that you have been trained in how to handle pesticides safely as described in the Worker Protection Standard (WPS) or that you are not required to take this training." As proposed, the AHETF would ask four comprehension questions on this eligibility criterion and share a link to WPS training with interested exempt workers.

Ms. Lydon discussed those monitoring units—M8, M17 and M1—that resulted in EPA requesting follow-up actions. Regarding Subject M8, Page 54 of the study states, "The subject placed his bare hands into a bag of sulfur to feel the powder and then wiped his hands on the ground." The study sponsor clarified, "The incident occurred so quickly there was no opportunity for intervention … The product label requires protective eyewear and chemical-resistant gloves while mixing/loading but does not anticipate this kind of incident." EPA noted that after M8 placed his bare hands into sulfur and dry-washed his hands in the soil on the ground, the Study Director designee and medical professional assigned to observe M8 should have directed him to immediately wash his hands with water, consistent with the product label. The study sponsor should have reported to the IRB that M8 placed his hands in the bag of sulfur, as well as the deviation of M8's not washing his hands consistent with the first aid statements on the label. As a follow-up action to monitoring unit M8, EPA requested that the study sponsor complete the following three actions in July 2016 or before. First, contact the assigned observer for M8 and the Study Director designee and inform them that the AHETF should have asked M8 to wash his hands with water immediately, consistent with the label. The purpose of doing this is to influence future actions and promote adherence to the label. The AHETF also should contact subject M8 and notify him that (1) he should not place his bare hands into bags of sulfur or other pesticide products and (2) if this occurs again, he should wash his hands immediately with water for the timeframe noted on the label. Finally, the AHETF should share this example of actions the research team should have taken with the Study Director, Study Director designees, observers and assigned medical professionals for the remaining studies. The AHETF reported that it already has completed all of these actions as requested.

Regarding Subject M17, Page 12 of the study states that "Subject M17 (5/28/14) did not wear eye protection when loading the first tank load of sulfur. He did wear his goggles for subsequent loads. Effect: No negative impact or adverse effect to the subject was observed. A noncompliance Issue/Deviation Submission was sent to the SAIRB [Schulman Associates IRB] on 6/2/14." The AHETF outlined corrective measures that are appropriate and should apply to the remaining studies. As the study sponsor suggested, the Study Director should remind participating subjects just prior to handling the product to wear all required PPE, remind the observers to be diligent in assuring that all required PPE is used, and double-check each subject before he handles test substances to assure that all required PPE is used.

Regarding monitoring unit M1, the study states the following: "After the first load, there was visible powder on the subject's face and clothes, and the subject complained of eye irritation. A face wash was performed, and the subject rinsed his right eye with his own eyewash kit and went back to work. He indicated that eye irritation and the need to flush his eyes is common when working with sulfur. He did not have any further issues with eye irritation for the rest of the monitoring activity." M1's actions were consistent with label instructions to rinse the eye. The subject wore goggles prior to reporting the eye irritation and continued to do so after the eyewash while mixing and loading. EPA considered whether eye irritation should have been reported to the IRB as an "unanticipated problem." SOP 11.F.2 states that the Study Director is required to report events that are unanticipated (not cited in the protocol) and possibly related to the study test substance or procedures. The protocol discusses the risk of exposure to surrogate chemicals and states that precautionary statements (e.g., related to eye irritation) should be discussed with subjects. As a result, the obligation to report the eye irritation to the IRB was not clear. Although M1 "indicated that eye irritation and the need to flush his eyes is common when working with sulfur," in the interest of full disclosure and out of an abundance of caution, the AHETF should have reported the irritation to the IRB and explained the situation. In hindsight, when reviewing the protocol,

EPA could have suggested asking subjects if they had experienced previous adverse reactions or irritations to the surrogate pesticides to be used. Page 43 of the study states that monitoring unit M1 "was given the Study Director's phone number to call if he did experience any further irritation; no calls were received. A follow-up phone call was made by the Study Director two days later; however, the subject could not be reached and did not return the call." EPA should ensure that future protocols state, "If a subject experiences adverse reaction, the Study Director should try to reach the subject at least twice to determine health status as it relates to the adverse reaction."

Regarding personal exposure results for subjects, the consent form asks subjects if they want to receive their personal study results. Results were requested by 17 of 19 subjects in AHE80. The Study Director sent the results to 16 subjects via first class mail. One subject did not provide an address, and the AHETF did not have a telephone number for the subject. Two sets of results were returned as undeliverable. In summary, 14 of the 17 subjects who requested their personal results received them. When reviewing future protocols, EPA should request that the following provisions be included. First, Study Directors should request the phone numbers of subjects who complete the consent process in case the Study Director needs to reach subjects regarding the study or follow-up actions. When personal study results are mailed to subjects and returned as undeliverable, the Study Director should call at least twice to try to reach affected subjects to share personal results via telephone. If the Study Director reaches the subject, he should confirm the address and resend the results if the initial address was incorrect.

Regarding heat index monitoring, Page 57 of the study reports the following information. The heat index was monitored approximately hourly after the ambient temperature reached 70 degrees Fahrenheit during monitoring. The Study Director immediately terminated the monitoring of M6 on obtaining a reading of 107 degrees Fahrenheit before the subject could load the spray rig that was arriving to be filled. The study reports, "During the period 0931–1030, the subject (M6) worked only 7 minutes on one tank load, completed his last mixing/loading at 1001, and was at rest the remaining time." SOP 11.G.5 was followed with one exception. The Study Director is supposed to inform all study observers at the start of the study of the current Heat Index (Apparent Temperature) Category. The observer is supposed to be informed if or when the Heat Index Category subsequently changes. In practice, the observer started weather monitoring at the first opportunity after observing the first mixing/loading or when it felt warm enough to merit it. This is a protocol deviation. EPA asked the AHETF to pay close attention to and follow this aspect of SOP 11.G, as well as the rest of the SOP, in its studies that have not yet been initiated or completed.

Regarding protocol amendments, the protocol was amended six times after it was signed. The study sponsor confirmed that the IRB approved amendments prior to implementation. EPA's ethics review discussed specific components of Amendments 2, 3, and 4, given their potential impact on ethical considerations. As discussed in the ethics review, the amendments did not negatively affect the rights and/or health and safety of subjects. EPA noted that Amendments 1, 2, 3 and 5, which were submitted for IRB review, already had desired "effective dates" on them, although they had not been implemented. For Amendments 4 and 6, the Study Director identified the effective date as the "IRB approval date" on the application. When applying for IRB approval of a protocol amendment, if the study sponsor must include an effective date on the protocol amendment form, EPA recommends and requests that the study sponsor insert "IRB approval date" as the effective date. Unless a research subject faces an immediate hazard, protocol amendments cannot be implemented prior to approval by the IRB. With regard to IRB oversight, the overseeing IRB reviewed and approved the initial protocol and six amendments. Also, four reported deviations were reviewed and acknowledged by the IRB. EPA identified two other nonreported deviations, which were addressed in follow-up actions for the AHETF.

Regarding documentation, the AHETF satisfied the requirements of 40 CFR Section 26.1303.

In summary, EPA identified the following follow-up actions for the AHETF as a result of study AHE80:

(1) The AHETF should begin using the following updated inclusion criterion in both protocol and consent forms, beginning in August 2016, for monitoring units not yet initiated in other AHETF studies to which the criterion applies: "Confirm that you have been trained in how to handle pesticides safely as described in the Worker Protection Standard (WPS) or that you are not required to take this training."

(2) The AHETF also should contact the assigned AHETF observer for monitoring unit M8 and the Study Director designee and inform them that the AHETF should have asked M8 to wash his hands with water immediately, consistent with the label. The purpose is to influence future actions and promote adherence to the label.

(3) The AHETF should contact subject M8 and notify him that (1) he should not place his bare hands into bags of sulfur or other pesticide products and (2) if this occurs again, he should wash his hands immediately with water for the timeframe specified on the label.

(4) This example of actions the research team should have taken should be shared with the Study Director, Study Director designees, observers and assigned medical professionals for remaining AHETF studies.

(5) As the AHETF suggested, Study Directors should continue to remind subjects to wear all required PPE, remind observers to ensure that all required PPE is used, and double-check each subject before he handles test substances to ensure that all PPE is used.

(6) For the remaining studies, the AHETF should request subjects' phone numbers in case the Study Director needs to reach them.

(7) The Study Director should pay close attention to and follow the SOP section 11.G, which states the Study Director will inform all study observers at the start of the study of the current Heat Index Category. The observer will be informed if or when the Heat Index Category changes.

(8) When applying for IRB approval of amendments, the study sponsor should insert "IRB approval date" as the effective date. Unless a subject faces an immediate hazard, the IRB must approve amendments prior to implementation.

EPA also identified the following three follow-up actions that the Agency should implement:

(1) For future protocols that require that interested subjects receive personal study results, EPA should request that the protocol include the following guidelines: When personal study results are mailed to subjects and returned as undeliverable, the Study Director should call at least twice and try to reach affected subjects to share the personal study results via phone. If the Study Director reaches the subject, the Study Director should confirm the address and resend the results if the initial address was incorrect.

(2) EPA should ensure that future protocols include the provision that if a subject experiences adverse reaction or irritation, the Study Director should call at least twice to try to reach the subject to determine health status as it relates to the adverse reaction.

(3) EPA should ensure that future protocols include the provision that Study Directors should request the phone numbers of subjects who complete the consent process, in case the Study Director needs to reach subjects regarding the study and/or follow-up actions.

EPA is of the opinion that Study AHE80 met the substantive acceptance standards as identified under 40 CFR Sections 26.1703 and 26.1705, as well as the obligations of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), Section 12(a)(2)(P).

EPA found that all subjects were at least 18 years of age and male. Pregnant or nursing women were excluded as required. The ethical conduct of the research had no significant deficiencies that would prevent EPA reliance on the study. EPA identified follow-up actions for both the study sponsor and the Agency. The protocol was executed as amended, and deviations did not compromise the rights of subjects. Finally, the subjects were fully informed, and their consent was fully voluntary, without coercion or undue influence.

Ms. Lydon concluded that the available information indicates that Study AHE80 was conducted in substantial compliance with Subparts K and L of 40 CFR Part 26.

Board Questions of Clarification—Ethics

Dr. Gary Chadwick, HSRB member, responded to two issues raised in the EPA Ethics Review. One person had reported having a previous adverse reaction to the active ingredient handled, which he suggested as a future criterion for study exclusion. Dr. Chadwick also suggested the following wording for the consent form: "not required under Worker Protection Standard regulation." Ms. Lydon replied that EPA would recommend that the study sponsor incorporate the criterion into future consent forms.

Dr. Gbur asked for more information about the certification process by which workers can become exempt from WPS training requirements. Ms. Nancy Fitz, OPP, who is a WPS expert, responded that applicators of restricted use pesticides can be certified by different programs administered by states, tribes and federal agencies that meet EPA standards. Some states require certified applicators to pass a written examination. Such programs might not include practical experience but do include more in-depth training in interpreting product safety labels than is provided by WPS training. Crop advisors generally are certified by programs that are administered by states or agronomy organizations and that are approved by EPA or the state. Such programs include all of the safety information training provided by WPS training, but Ms. Fitz did not know if they include either an exam or field experience.

Public Comments

Mr. Downing indicated that no requests had been received by EPA in advance of the meeting to provide public comments. Dr. Dawson asked members of the public participating via teleconference to provide comments. Hearing no response, Dr. Dawson invited Dr. Maddalena to present his scientific review.

Board Discussion—Science

Drs. Maddalena and Gbur reviewed the scientific and statistical content of AHE80.

Dr. Maddalena read the two science charges into the record:

- Was the research reported in the Agricultural Handler Exposure Task Force (AHETF) completed monograph report and associated field study report for AHE80 faithful to the design and objectives of the protocol?

- Did the research generate scientifically reliable data, useful for assessing the exposure of individuals who mix and load conventional pesticides formulated as wettable powders?

First, Dr. Maddalena offered his observations on the field study report, which he described as a thorough, high-quality account of a difficult project. The report nicely documented all of the challenges encountered by the researchers and the strategies that they used to address those challenges. The methodology of the study was sound and well-validated. He also noted that the exceptional thoroughness of the observation section was especially helpful.

Dr. Maddalena also observed that two of the subjects—10 percent of the 21-subject study cohort—carried out the protocol in noncompliant garments although the subjects had been given the correct, fully protective garments. Dr. Maddalena emphasized that this is not a criticism of the protocol or of the study itself, but the incident does serve as a reminder of compliance problems that are sure to be encountered in real-life situations.

The monograph presented a clear, well-documented description of all aspects of the wettable powder mixing and loading scenario, along with a nicely integrated presentation and analysis of the data. The report also provided a complete rationale for the study, including an account of the inadequacies of the existing database for this scenario.

The report articulated the key assumptions that underlie the study:

- **The independence of active ingredients.** The report asserted that exposure is not determined by the chemical properties of the active ingredient itself, but instead by physical factors. Because it is unlikely that chemical properties of active ingredients are irrelevant at all levels of exposure, Dr. Maddalena recommended that the task force revise the wording of this section.

- **Issue of proportionality.** Exposures are related to the amount of active ingredient handled.

Dr. Maddalena also called the Board's attention to earlier concerns raised by the previous HSRB review; he examined the ways in which the current study may or may not have addressed those concerns.

The HSRB had recommended that monitoring units be added to the study in a way that would populate the tails of the distribution of ingredient handled to provide more statistical power. Although the current study added 20 monitoring units to the original five units, the investigators ultimately were unsuccessful at recruiting monitoring units at the lower end of the range of AaiH. This truncated test range weakened the statistical power of assessments of the relationship between exposure and amount of product handled.

In the original study, the Board questioned whether representative diversity existed in exposures across regions. The current study addressed this issue satisfactorily.

The Board recommended that future studies cover all three mixing subscenarios. The current study still does not provide much diversity in the mixing scenarios.

The Board also raised questions about the relevance of the equipment and processes used in the test scenario to the range of possibilities in the field. The current study also did not manage to test the full extent of what is possible.

The study did address this concern to some extent, however, by including a informal survey of experts in the field; these experts agreed that the scenario was representative of possibilities in the field.

In summary, the biggest challenge in the current study was the inability to recruit enough subjects to obtain a truly random sample. Investigators also were unable to test the full diversity of scenarios (equipment, mixing methods, kinds of active ingredients, amount handled) likely to be encountered in the field. Both the monograph and the field report, however, are transparent about these limitations and the strategies used to handle them. EPA is aware of the issues and accepts them as the challenge of performing field work. Although the data do not meet all of the scientific objectives, they are nevertheless scientifically useful; they are significantly better than data currently available in the Pesticide Handlers Exposure Database.

Dr. Gbur provided his review of the statistical aspects of the study.

Although there was some question whether or not the scientific charge referred both to inhalation and dermal exposure, or only to dermal exposure, Dr. Gbur discussed the data for both dermal and inhalation exposure. Echoing Dr. Maddalena's comments, Dr. Gbur complimented the Task Force on the clarity of its data presentation.

A primary objective of the study was to estimate exposure statistics to within threefold accuracy. The statistics for dermal exposure were within threefold accuracy, thus satisfying the objective. Subject 13 was considered an outlier because of the unusually small dermal exposure value for that subject; the results of the data analysis for dermal exposure were similar, however, whether or not Subject 13 was included in the analysis.

In contrast to the data on dermal exposure, the inhalation exposure of Subject 13 was not an outlier, but well within the other subjects' range. Although the EPA review did not consider threefold accuracy a primary objective for inhalation exposure statistics in this study, the fact that the inhalation exposure statistics were not, in fact, within threefold accuracy is nevertheless a cause for concern.

A secondary objective of the study was to probe the relationship between exposure and amount of material handled, specifically to test whether these data showed complete proportionality (slope of 1) or complete independence (slope of 0).

When Subject 13 was included in proportionality analyses of dermal exposure relationships to amount of material handled, the statistics could not distinguish between proportionality and independence. Exclusion of Subject 13 did result in proportionality, but the power requirement of 80 percent still was not satisfied. Proportionality analyses of inhalation exposure also did not meet the 80 percent power requirement.

Dr. Dawson asked whether inhalation exposure data might be more subject to variability because, in addition to the amount of material handled, variable methods for handling the material can affect exposure. In contrast, dermal exposure is more likely to be predictably proportional to the number of bags that are handled.

Dr. Maddalena agreed, noting that even where overall handling methods are similar, occasional "powder puff" events cause bursts of inhalation exposure. With dermal exposure, all subjects tend to receive similar doses of material on the outer layer of their garments. He also emphasized that these considerations apply explicitly to exposures arising from mixing the material, not to the kinds of exposures encountered in other contexts.

Dr. Dawson noted that the analytic difficulties posed by the variability of inhalation exposure values might provide an additional rationale for a greater focus on dermal exposure. Dr. Maddalena

replied that a goal of the study was to characterize different sorts of exposures. Even if the variability of inhalation data poses analytical and statistical difficulties, both Dr. Maddalena and Dr. Gbur agree that the data still are of scientific use.

Dr. Maddalena asked the Board to approve the following response to the first scientific charge question: The research reported in the Task Force-completed monograph and associated field report was faithful to the design objectives of the protocol. The Board approved the response unanimously.

The wording of the formal response to the second scientific charge was discussed. Although the exact wording was not finalized at the time of the discussion, the Board gave unanimous approval to the general sentiment that the research generated "scientifically reliable data useful for assessing the exposure of individuals who mix and load conventional formulated powders, but with limitations." Drs. Gbur, Maddalena and Dawson planned to refine the final wording of this response for consideration by the Board during the discussion the following day, before the end of the meeting. Mr. Downing approved this plan.

Board Discussion—Ethics

Dr. Chadwick reviewed the ethical aspects of AHE80. Dr. Chadwick read the following charge into the record:

> Does the available information support a determination that the research was conducted in substantial compliance with 40 CFR Part 26, Subparts K and L?

Dr. Chadwick stated that the protocol, with supporting documentation, was submitted to two IRBs. Two IRBs were involved because the first, independent IRB was acquired by another company, Schulman Associates, which then assumed IRB responsibilities. Both IRBs are accredited. Dr. Chadwick had reviewed the minutes of the IRB meetings and all correspondence between the investigators and the IRB. He stated that the IRB reviewed the protocol before the project began and reviewed and approved amendments and reports submitted during the study. All of these reviews and approvals met the standards 40 CFR Part 26, Subpart A. Informed consent materials were revised several times; a Spanish-language consent form also was included.

Dr. Chadwick thanked the Task Force for listening to the Board's earlier concerns and incorporating the Board's suggestions into the current study. He complimented the Task Force for the high standard of ethical conduct incorporated into the study design. The informed consent form contained adequate information for the 21 enrolled subjects, explaining the risks, discomforts and benefits of participation. The form also explained the right to withdraw; this appears to have been effectively communicated because two people did withdraw from the study. The risk/benefit ratio was deemed acceptable; the risk appeared to be minimized and was justified by societal benefits. The selection of study participants, both English and Spanish speaking, was equitable. No children or pregnant women were enrolled. Dr. Chadwick also suggested as a topic for future discussion the possibility that previous experiences of potential subjects with discomforts or reactions to the material in question might be a disqualifier for participation in future studies.

The documents, particularly the field study report, indicated that the study was conducted in accord with the regulatory standards of 40 CFR Part 26, Subparts K and L, as well as EPA Good Laboratory Practice Standards (40 CFR Part 160), and complied with FIFRA Section 12(a)(2)(P). The research conducted in California met the requirements of the California EPA Department of Pesticide Regulation and the California Committee for the Protection of Human Subjects. Researchers who interacted with participants had the required ethics training to conduct these studies.

Dr. Chadwick asked the Board to approve the following response to the charge: The studies were conducted in substantial compliance with 40 CFR Part 26, Subparts K and L. Board members agreed unanimously to the response.

Closing Remarks

Mr. Downing indicated that the meeting would reconvene on July 13, 2016, at 1:00 p.m. EDT. The second topic of the meeting, which is a study similar to the topic of today's meeting but involves mixing/loading using water-soluble packets, will be discussed. Mr. Downing requested that the Board members join the meeting at 12:50 p.m. to ensure a prompt start.

Mr. Downing recessed the meeting for the day at 4:11 p.m. EDT.

Wednesday, July 13, 2016

Convene Public Meeting

Mr. Downing convened the second day of the meeting at 1:00 p.m. and welcomed Board members, EPA colleagues and members of the public. Mr. Downing reiterated the Agency's appreciation of the Board's time and efforts and his appreciation of his EPA OPP colleagues for their efforts.

Mr. Downing noted that in his role as DFO under FACA, he serves as liaison between the HSRB and EPA and is responsible for ensuring that all provisions of FACA are met regarding the operations of the HSRB. Also in his role as DFO, he works with appropriate Agency officials to ensure that all appropriate ethics regulations are satisfied. HSRB members were briefed on provisions of the federal ethics and conflict-of-interest laws and have completed a government financial disclosure report, which has been reviewed to ensure that all ethics requirements are met.

Mr. Downing informed Board members that an interesting topic would be discussed during the second day of the meeting. Supporting documents for the meeting are available on the HSRB website.[2] He noted that agenda times are approximate and that adequate time will be allowed for Agency presentations, public comments and the Board's deliberations.

Following EPA presentations, time has been allocated for the Board to ask clarifying questions. Time also has been allocated for public comment. Mr. Downing noted that no individuals had provided comments in advance of the meeting, and he had received no requests to provide public comments during the meeting. The Chair will call for public comments during the public comment period. Such comments should be limited to 5 minutes.

In accordance with FACA requirements, 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 calendar days. The approved minutes will be available on the HSRB website. The HSRB also will prepare a final report in response to the charge questions posed by the Agency, which will

[2] The HSRB website is available at www.epa.gov/osa/human-studies-review-board.

include the Board's review and analysis of materials presented and the Board's advice and recommendations to the Agency. The final report will be available on the HSRB website.

Virtual Meeting Operations

Mr. Downing and Dr. Dawson reviewed guidelines for virtual participation in the meeting. Mr. Downing indicated that the chat feature of Adobe Connect would not be used, the hand-raising feature should be used by Board members to request the floor to speak, and the approval/disapproval feature should be used by Board members for voting. Dr. Dawson reminded participants that their telephone lines should be muted when they are not speaking. When speaking, participants should identify themselves for accurate recordkeeping in the meeting minutes.

Introduction of Board Members

Mr. Downing conducted a roll call of the Board members. Dr. Dawson welcomed the Board members and asked them to introduce themselves, providing their names, affiliations and areas of expertise. The Board members completed their introductions. Dr. Suzanne Rivera, who had been unable to attend the meeting on July 12, was in attendance on July 13.

Opening Remarks

Dr. Dawson indicated that Dr. Schonfeld was unable to attend the second day of the meeting.

Follow-up Discussion From the Previous Day

Dr. Maddalena indicated that he did not disagree with the Board's content of the proposed response to the charge question regarding whether the research had generated scientifically reliable data, but he requested that the Board review the wording of the response. "Variability" does not have the same meaning as "uncertainty." The high variability in monitoring data led to uncertainty in estimating inhalation exposures. Dr. Gbur suggested clarifying whether the Board is referring in its response to variability in the monitoring data, which cannot be reduced, or variability in the estimates of inhalation exposures, which results in uncertainty in the exposure estimates. High variability in the monitoring data led to difficulty in estimating the statistics that EPA will use to characterize inhalation exposure with the degree of certainty that was the primary objective of the exposure analysis. The threefold relative accuracy benchmark for the inhalation exposure analysis was not met. Dr. Dawson noted that the study was designed to capture variability in day-to-day practices. Dr. Maddalena proposed the following response to the charge question:

> The research generated scientifically reliable data, useful for assessing exposures related to conventional pesticides formulated as wettable powders, subject to recognition of the following: (a) limited diversity in scenarios; (b) failure to confirm proportionality of exposure with AaiH; and (c) <u>uncertainty in estimates of inhalation exposures due to high variability</u>.

The text that differed from the response last considered by the Board is underlined.

The Board discussed the wording of the response. Dr. Gbur recommended spelling out "AaiH" for clarity. Dr. Kenneth Ramos, HSRB member, proposed formatting the response as two separate sentences, one responding affirmatively to the charge question and one describing limitations of the usefulness of the data. He also asked for clarification of limitation (a). Mr. Downing suggested providing

more detail on limitation (a) in the Board's final report. In response to a question from Dr. Maddalena regarding whether readers might focus only on the Board's responses to charge questions in the final report, Mr. Downing indicated that OPP will study the Board's final report in detail, which Ms. Lydon confirmed. Dr. Ramos then proposed simplifying the response to read, "subject to the limitations as noted in the Board's report." Dr. Maddalena commented that limitations (a), (b) and (c) could be headings in the report. Dr. Jewell H. Halanych, HSRB member, initially favored retaining the limitations in the text of the response, but changed her vote to agree with the other Board members, who voted unanimously to provide a more generic response that would state that the limitations are discussed in the report.

Completed Study and Monograph Report for Agricultural Handler Exposure During Mixing/Loading of Pesticide Products in Water-Soluble Packets (Agricultural Handlers Exposure Task Force)

EPA Science Review Highlights

Mr. Crowley provided a science review of the above study (heretofore referred to as AHE120) and the AHETF's pesticide study handler scenario of mixing/loading of pesticide products in water-soluble packets. The scenario is defined as placing water-soluble packets directly into a spray application equipment tank water or into slurry or premix tank water and then transferring the spray mixture to the application equipment; the scenario does not include spray application. Water-soluble packets are an engineering control—a term with regulatory implications—that is designed to reduce worker exposure to the packet contents, which can be various formulations. The study objectives were to capture the variability of expected dermal and inhalation exposures for workers who are mixing and loading water-soluble packets and to design the study to meet quantitative analytical objectives regarding the accuracy of exposure estimates and the ability to distinguish proportionality between dermal exposure and the amount of AaiH.

The general study design used a clustered sampling approach to satisfy study objectives while minimizing costs and number of participants. The HSRB approved the protocol in 2010, which proposed a 5 × 5 configuration (i.e., five clusters of five participants each), and such factors as location and employer were diversified to obtain the desired exposure variability, with randomness incorporated into the recruitment process to minimize selection bias. Dermal (i.e., hands, head and body) and inhalation exposure were monitored using hand washes, face/neck wipes, whole-body dosimeters in two parts, and an Occupational Safety and Health Administration versatile sampler with an air pump. Mr. Crowley presented data on the LODs and limits of LOQs of the AHE120 exposure monitoring methods. He indicated that more of the monitoring results for dermal and inhalation samples were less than the LODs and LOQs than for AHE80 because exposures were lower.

The AHE120 protocol was amended to aid in finding study participants, increase the limit of thiophanate-methyl (TPM) that could be handled (although the original limit was not exceeded), and exclude work practices that were inconsistent with the use of water-soluble packets as an engineering control. EPA found these amendments to be reasonable. No protocol deviations were reported.

Quality assurance and quality control practices were adhered to. As in AHE80, quality assurance procedures ensured that the study followed EPA's Good Laboratory Practice Standards, including training research personnel and performing site and equipment inspections. Negative (i.e., laboratory or field blanks) and positive (i.e., laboratory spikes or field fortifications) control samples were collected. Some blanks had detectable results, but no systematic contamination was found, and no corrections were made for blanks. Laboratory recoveries were close to 100 percent, and average field fortification recoveries ranged from 71.1 to 140 percent. In some instances, calculation of average field fortification recoveries excluded unusual results. Monitoring results were adjusted to account for field recoveries that differed

from 100 percent, with a maximum adjustment factor of 1.2. Plotting the coefficient of variation versus the mean for field fortification triplicates reveals that most results showed acceptable recovery and variability.

Mr. Crowley described scenario characteristics. The scenario activity involved filling a tank (or intermediate holding tank or bucket) partially with water, adding the water-soluble packet to the water, mechanically agitating and recirculating to dissolve the packet and mix the formulation in water, transferring the mixture to pesticide application equipment if mixed in an intermediate tank, and adding water as necessary to the desired concentration after the packet was dissolved. For regulatory risk assessments, all data should represent compliance with product labels, but monitoring for nine workers was either not completed or completed and analyzed but not included in the final data set because of circumstances inconsistent with product label language (i.e., broken packages or mixing tank additives before products) or practices about which current labels lack specific language (i.e., use of baskets or strainers or overhead water circulation). As a result, the number of monitoring units in the final data set was reduced from 25 to 16. In addition, the risk assessment will note that the labels need to be revised or amended to be consistent with the practices under which the risk assessment data were gathered. AHE120 Appendix G lists best practice mixing/loading instructions for water-soluble packets that EPA will share with stakeholders to finalize the labels. Other scenario characteristics include that the workers were all male but were variable in age, work experience, weight and employment status. The sampling locations and dates were expanded geographically from five to 10 sites and temporally to 3 years to meet recruitment challenges, resulting in 10 clusters with one to three monitoring units per cluster. Sampling took place from 2011 through 2014 and occurred in North Dakota/Minnesota, Florida, Mississippi/Louisiana and California. The study's goal was to monitor multiple types of mixing and loading, but most of the mixing occurred directly in the application tank. The amount mixed and loaded—as measured by number of tank loads, gallons of solution prepared, time and AaiH—was diverse.

Exposure monitoring results were calculated for hand dermal exposure (utilizing EPA's convention of doubling hand exposure to account for potential method collection inefficiencies, i.e., "MEA factor"), head dermal exposure (utilizing EPA's convention of doubling head exposure to account for potential method collection inefficiencies, i.e., "MEA factor"), body exposure (sum of two whole-body dosimeter sections), and inhalation exposure (adjusted by the breathing and pump rate), adjusting for average recovery of the corresponding field fortification matrix and level.. Each worker's total dermal and inhalation exposures then were divided by the amount of active ingredient they handled. The MEA adjustment was used when dermal exposure represented 20 to 60 percent of total exposure, an approach contested by the Task Force in a recent submission that EPA is reviewing. The MEA-adjusted results for dermal exposure averaged 11.0 µg/lb ai (range = 0.476–64.7 µg/lb ai, P95 = 30.1 µg/lb ai). The contribution of dermal exposure to total exposure ranged from 4 to 78 percent, but the use of a dermal MEA adjustment factor is triggered by the average relative dermal exposure contribution, which was 34 percent. Inhalation exposure monitoring results were low and highly variable compared to dermal exposure, ranging from 0.000056 to 3.89 µg/lb ai (average = 0.583 µg/lb ai, P95 = 2.0 µg/lb ai). For illustrative purposes, Mr. Crowley presented the exposure monitoring results with the excluded data, which increased the average dermal exposure to 97 µg/lb ai and the average inhalation exposure to 2.5 µg/lb ai.

The exposure monitoring results—normalized to the amount of AaiH (i.e., unit exposure)—were analyzed by three methods: empirical estimates (i.e., simple statistics), simple random sample (i.e., a log-normal distribution of data that were assumed to be independent), and mixed model (i.e., a log-normal distribution that incorporates potential correlation of data within clusters). The dermal and inhalation unit exposure monitoring results when plotted more closely followed a log-normal than a normal distribution. Unit dermal and inhalation exposure data plotted versus cluster number, which describes spatial and temporal proximity, illustrated that the AHETF analysis properly accounted for cluster effects. EPA

agreed with the Task Force that considering the data structure, a log-normal mixed model is most appropriate for statistical analysis. CIs were determined using bootstrap simulations. The geometric standard deviation unit exposures were 3.39 µg/lb ai (95% CI = 2.22–5.29 µg/lb ai) and 15.1 µg/lb ai (95% CI = 5.33–43.7 µg/lb ai) for dermal and inhalation exposure, respectively, with ICCs of 0.00 and 0.54 µg/lb ai for dermal and inhalation exposure, respectively.

The primary study objective, meeting the accuracy benchmark of threefold relative accuracy, was met for both MEA and non-MEA dermal exposure, but inhalation exposure showed much higher variability. The secondary study objective, designing the study to distinguish independence from proportionality between dermal exposure and the amount of AaiH with 80 percent statistical power, is used to assess whether more data are needed and is of lessor importance. A regression slope of 1 indicates proportionality, whereas a slope of 0 indicates independence, and a width of 95 percent CI of 1.4 or less is consistent with meeting the study design objective of 80 percent statistical power. The slopes of the unit dermal and inhalation exposure regression analysis were both much closer to 1 than 0, and the power objective was met for the dermal monitoring results (width = 0.68), but not for the inhalation monitoring results (width = 2.01).

Regarding regulatory exposure assessments, the use of the data is contingent on changing the product labels, which currently lack sufficiently clear instructions, to match the activities of the workers in this study. EPA has begun the process of working with stakeholders to develop clear, concise and implementable label language. The data will represent compliance with the revised product labels and will represent the variability of expected exposure when water-soluble packets are used. The data would be used in the regulatory review process for new and current chemicals to quantify exposure during mixing/loading of pesticides in water-soluble packets, which would be compared to the relevant chemical-specific toxicity benchmarks.

Mr. Crowley concluded that EPA determined that the study design was acceptable, monitoring methods were representative of the state of the science, the analysis of primary and secondary objectives was acceptable, data are recommended for use in regulatory assessment with AaiH normalization, and data use is contingent on product label revisions.

Board Questions of Clarification—Science

Dr. Maddalena noted that multiple active ingredients were included in the study. He asked whether a statistical analysis was performed to justify the assumption that monitoring results were independent of the active ingredient used. Mr. Crowley responded that given the diversity of locations and ingredients, the study had insufficient power to perform such a test. Dr. Maddalena recognized the value of the study's goal of maximizing the variability of testing conditions.

Dr. Ramos asked Mr. Crowley to comment on using a surrogate for active ingredients in the study protocol. Mr. Crowley clarified that the active ingredients are referred to as "surrogates" because the results of this study, if approved by the HSRB, will be used in risk assessments as surrogates for active ingredients that were not tested but are used with similar equipment and activities. The materials tested were, however, actual pesticide active ingredients. Chemical differences among active ingredients are controlled for using field fortification samples. Matrix spikes confirm that a particular active ingredient can be measured accurately in a given matrix (e.g., hand wash samples and whole-body dosimeter suits). Dr. Ramos supported the inclusion of positive controls in the study design but indicated that questions remain regarding chemical-specific effects.

Mr. Crowley confirmed to Dr. Ramos that the excluded versus nonexcluded populations referred to the fact that only 16 monitoring units were included in the statistical analysis although 25 monitoring units began monitoring.

Dr. Gbur noted that approximately one-half of the clusters consisted of a single monitoring unit. In estimating variability in a study with a clustered sampling approach, variability generally is assessed both within and between clusters, but in this study, only one cluster produced a within-cluster estimate of variability. Mr. Crowley responded that variability estimates and regression analysis results were almost identical when the monitoring units were treated independently compared with when a mixed model was used, as expected with few monitoring units in each cluster. Because more clusters were needed to meet recruitment goals than specified in the original study design, the actual study design was more similar to a 1×15 than a 5×5 sampling approach. Dr. Larry Holden, statistical consultant to the Task Force, added that data always are analyzed both with and without the assumption of within-cluster correlation, but in this study, the results of the two analyses were approximately the same because the data essentially were independent. The correlation is measured for use in bootstrapping to determine the CI from the data. In response to a further question from Dr. Gbur about standard errors in the variability estimate, Dr. Holden stated that the data set was too small to estimate the standard errors of the variance components.

EPA Ethics Review Highlights

Ms. Lydon presented highlights from EPA's ethics review of study AHE120. Her presentation addressed the following topics: actions to address HSRB comments on protocol, recruitment and informed consent, PPE and medical professionals, compensation, eligibility criteria and WPS training, monitoring units resulting in follow-up actions, exposure results for subjects, heat index monitoring, protocol amendments and effective dates, IRB oversight, documentation; and findings and conclusions.

The HSRB reviewed the draft protocol during its meeting on October 27–28, 2010. Attachment 4 to EPA's ethics review summarizes the study sponsor's actions to address HSRB comments on the draft protocol. Ms. Lydon presented examples of the changes made in response to comments. Section 17 of the protocol states that "Individual results requested by subjects will be communicated in accordance with SOP AHETF-11J." SOP 11J describes how personal study data will be presented to and shared with subjects who request their results. The study sponsor updated the informed consent process to address this topic. If a subject wants personal study results, there is a box on the consent form that can be checked, as suggested by the HSRB, and a form titled Request for Personal Study Results also is completed. Subjects can receive their results in English or Spanish, depending on their preference.

In response to comments, the AHETF explained the process to verify the accuracy of Spanish translations. In the previous day's meeting, Ms. Lydon had outlined this process and the translation review project when discussing AHE80. The same process applies to AHE120. The AHETF undertook a translation review project to ensure that Spanish translations were accurate. The AHETF identified bilingual pesticide safety trainers in different regions of the country. The AHETF sent the bilingual trainers both English and Spanish versions of the consent form, recruitment flyer, California bill of rights (for the California reviewers), and other support documents and asked whether they had any edits regarding the Spanish translations. They also sent to them a list of agricultural terms in English likely to be used in protocols at the time and asked for their translations of those terms based on the region in which they lived. Six individuals from different regions of the country reviewed the documents and provided feedback, and the AHETF incorporated their feedback. The AHETF hired a Spanish-fluent senior scientist who took into account the results of the translation review project. She translates into Spanish all consent forms and other materials. The AHETF submits her work to the overseeing IRB, which requests that a certified translator review and comment on the translation and certify the translation with a letter of accuracy. The Spanish translation follows the approved English version.

Regarding risk of exposure to surrogate chemicals, both the protocol and consent form were revised to identify this risk.

The HSRB wanted the overseeing IRB, SAIRB, to have the full IRB review major changes to the protocol instead of using an expedited process. SAIRB ultimately reviewed about one-half of the amendments through the full board and one-half through expedited procedures.

Regarding PPE, an eligibility criterion states that subjects must usually wear the PPE listed on the label of the pesticide products that they will mix and load and must confirm that they would not normally wear PPE not required by the label. To assess eligibility, the AHETF asks potential subjects what PPE they normally wear when handling pesticides so as not to direct potential participants to any particular answer.

As requested by the HSRB, both the SOP and consent form were revised to reflect that hand washes will occur before subjects smoke or eat. To address HSRB comments on refusal of medical treatment and associated criteria, the consent form, SOP 11.H.4 and the protocol were revised. The consent form states, in part, "You may refuse medical treatment unless you get sick from too much exposure to pesticides or from getting hot, or if the medical professional decides you are too sick to make a rational decision about getting medical treatment." The SOP and the protocol lay out specific criteria for the medical professional to use in determining whether a subject is competent to refuse medical treatment.

Regarding recruitment, some of the monitoring regions in this study overlapped with study AHE80 on wettable powders. Many employers used both wettable powders and water-soluble packets. Because of this, Protocol Amendment 4 was approved by the IRB and allowed simultaneous recruitment for both studies. As a result of that, the Universe, Master and Qualified Recruitment Lists for the two studies were combined for efficiency's sake. AHE120 discusses the three-phase process for recruitment in great detail. EPA's ethics review also includes several pages on recruitment. In summary, Phase 1 ultimately results in a list of qualified employers, Recruitment Phase 2 results in the list of potentially eligible employers, and Phase 3 results in the list of eligible employers. The study describes the recruitment process in detail as the study sponsor begins with the number of employers on the Universe List and ultimately arrives at the number of workers participating in the study. For example, the summary of recruitment details for North Dakota on page 39 of the study gives the progression beginning with more than 64,900 employers on the Universe List and ultimately arriving at five workers identified for participation in the study. After recruitment, the Study Director schedules and conducts informed consent sessions and begins to monitor study participants. Recruitment meetings occurred in all monitoring areas, and the AHETF confirmed that required information was covered. All growers signed the employer noncoercion statement before recruitment. EPA's ethics review compared the recruitment approach used in study AHE120 with the process identified in the protocol and SOPs. EPA found that the AHETF generally followed the recruitment outlined in the protocol and SOPs, with amendments approved by the overseeing IRB.

After recruitment, participating subjects completed the informed consent process and signed consent forms prior to monitoring. The Study Director met privately with each subject, reviewed the consent form section by section, and asked comprehension questions to document each subject's understanding. In Florida, three workers at one site and one worker at a second site opted to have a Spanish-speaking researcher present during their consent meetings. Subjects received copies of their signed consent forms. The AHETF mailed Subject M10 his consent form because he did not receive it on the day of monitoring as other workers did. Subjects were informed of the pesticide active ingredient and end-use product by the time they completed informed consent process. Consistent with the consent form and/or protocol, the AHETF reviewed with subjects the following information listed: how much of the product the subject might handle during the study, required clothing and PPE, the importance of washing hands before eating or smoking, other safety precautions that should be followed, specific risks associated with the end-use product as discussed on the label, and procedures to be followed both before the start of

the study and on the day of the study. Participating subjects signed the IRB-approved consent forms, which include the eligibility criteria written in plain English.

Regarding PPE, subjects wore the required PPE as specified on product labeling and in the protocol, as well as the outer clothing prescribed in the protocol.

A medical professional was present for the duration of each monitoring event and periodically checked subjects for heat-related illness. Attachment 10 to EPA's ethics review identifies the medical professional assigned to each subject.

Subjects received compensation consistent with protocol and the informed consent form—$20 for participating in the consent meeting and $80 for each day participating in the study.

The 16 monitored workers were males between 18 and 71 years of age. No female subjects volunteered to participate in the study. No changes were made to the recruitment process to exclude female subjects. In the previous four AHETF studies, one subject was female. The Study Director has been conducting mixer/loader and applicator exposure studies in production agriculture for more than 3 decades and has never encountered a female mixer/loader or applicator. The Study Director's field experience is that women are more likely to conduct harvesting work and agricultural reentry activities.

The work experience of the monitored workers ranged from one to approximately 50 years.

As discussed for AHE80, one of the eligibility criteria in the approved SOP reads as follows: "Be trained in safe pesticide handling procedures in accordance with the Worker Protection Standard (WPS) or equivalent Canadian regulations, or be exempt from such training." EPA noted the WPS criterion appears on the consent form as, "Confirm that you have been trained in pesticide safety or that you are not required to take this training." EPA would like this criterion updated on the consent form so that it reads, "Confirm that you have been trained in how to handle pesticides safely as described in the Worker Protection Standard (WPS) or that you are not required to take this training under WPS." One HSRB member had suggested during the previous day's discussion that the study sponsor may want to specifically reference the WPS. EPA agrees with this addition and added it to its recommendation on updating the consent form.

During the previous day's discussion, Ms. Lydon had reviewed the proposed four comprehension questions associated with this revised criterion. If the study does not begin on the same day as the consent meeting and if the subject is exempt from WPS training, the AHETF should email interested subjects a link to WPS training information.

A reportable event and unacceptable work practice occurred in AHE120. Water-soluble packaging is an engineering control designed to prevent contact between workers and the formulation (for example, wettable powder) in the packages. Water-soluble packets are designed to dissolve in water and release the formulation into the water without forming any type of dust or liquid aerosol that could contact workers. Breaching the packets to facilitate release of the powders is contrary to the intent of packaging the powdered formulation in water-soluble packets because it circumvents the engineering control properties of water-soluble packets.

During the early course of the study, as discussed earlier, the AHETF observed workers using procedures that they later realized circumvented the goal of water-soluble packets to reduce potential exposure. As described on page 58 of the study, some workers placed the water-soluble packets in removable baskets hanging from the open hatch or directly into the tank and then used streams of water from hoses to break open the water-soluble packets, causing visible amounts of airborne powder to be released from the mix tank where the mixer/loader was working. In a letter dated June 6, 2012, the

AHETF informed EPA of this issue. On June 7, 2012, the study sponsor filed a reportable event with the IRB associated with these actions. This was the only reportable event that the AHETF identified to the IRB. In the AHETF's June 21, 2012, conference call with EPA, California's Department of Pesticide Regulation, and the Canadian Pest Management Regulatory Agency, it was decided that directing water onto water-soluble packets in baskets in sprayer hatches would not be a supported practice. At that point, Protocol Amendment 6 requiring the removal of baskets before adding the water-soluble packets reflected this decision.

When the study sponsor observed different unexpected mixing methods later in the study and subsequently realized their effects on exposure, additional amendments were submitted to the IRB. Amendments 8 and 13 were based on observations of different mixing methods that also circumvented the engineering control and caused visible aerosols that exited the mixing tank. Amendment 13 modified the water-soluble packets mixing/loading instructions to reflect best practice techniques over a wide range of equipment and loading configurations. The unacceptable practices identified by the AHETF for nine monitoring units are listed in Attachment 12 to EPA's ethics review. After reviewing the description of the "unacceptable monitoring units," EPA asked the study sponsor to formally submit additional information to the Agency. The result is Appendix G to the study, which was provided to the HSRB in a separate file. EPA asked the AHETF about the years of experience of the workers identified as monitoring units M1, 2, 4, 5, 8 and 9 with regard to loading water-soluble packets. These workers directed water onto the water-soluble packets, and four of them used baskets while doing so. Except for subject M2, the workers had between 10 and 35 years of experience loading water-soluble packets.

Researchers confirmed that they had reviewed the following label information with these workers prior to their participation in the study and consistent with the informed consent form: how much of the product they might handle during the study, the clothing and PPE they must wear, the importance of washing hands before eating or smoking, and other safety precautions that should be followed. Consistent with the protocol, the specific risks associated with end-use products being handled also were reviewed and discussed directly from the label. . Page 14 of the protocol states that AHETF is supposed to ensure that all tank mix products are used according to the approved label and the study sponsor is supposed to remind workers of safe chemical handling practices. Page 30 of the protocol states that researchers will watch and take notes on worker activities and monitor the workers and environmental conditions to ensure safe working conditions. EPA noted, however, that neither the consent form nor the protocol actually require the AHETF to review the use directions for the surrogate chemicals with subjects. The protocol also states that the AHETF will monitor only those workers who are mixing/loading in accordance with all label, WPS and state regulatory requirements. As a result of the information learned during study AHE120, the study sponsor developed a standard set of loading instructions for water-soluble packets that are included in Appendix G. The AHETF developed the instructions in consultation with members of the Joint Regulatory Committee—including EPA, the Health Canada Pest Management Regulatory Agency, and the California Department of Pesticide Regulation—to provide best practices for handling and adding water-soluble packets to spray tanks. The goal of these instructions is to ensure that water-soluble packets are allowed to dissolve in water and prevent them from being ruptured by streams of water or other means.

The six monitoring units who used baskets, streams of water and/or overhead recirculation to rupture or agitate the water-soluble packets were monitored before the new instructions were completely adopted for use in the study. Before the AHETF developed the best practice mixing/loading instructions for water-soluble packets, the Study Director spoke with handlers M5 and M9 in the field at the end of their respective monitoring periods. This occurred when the Study Director recognized that the workers could reduce their exposure. Appendix G summarizes these conversations.

At the end of each monitoring period, based on observations during the monitoring, the Study Director advised subject M5 to first remove the basket in the hatch before loading water-soluble packets. This conversation occurred after the Study Director saw a coworker do this. At the end of the monitoring period, after seeing aerosols exit the tank, the Study Director advised subject M9 not to add overhead water to the tank until the water-soluble packets had dissolved. During monitoring unit 19, the Study Director asked workers carrying boxes containing water-soluble packets not to drop them on the ground, because dropping the boxes may have caused some packets to break open.

Study AHE120 indicates that, before the study was initiated, the AHETF was knowledgeable about the label directions for using water-soluble packets. The AHETF was not familiar, however, with practices that the individual agricultural handlers would use in the field that are not reflected on the label and about which the label is unclear or actually silent. Because water-soluble packets are an engineering control designed to prevent contact between workers and the wettable powder in the packages, the study sponsor did not anticipate that workers would use practices not listed on the label and that ultimately broke open the packages. In hindsight, one could argue that the AHETF should have investigated the work practices associated with water-soluble packets used in the field in advance of the study. The approved protocol states, however, that the study sponsor will "only monitor workers mixing/loading in accordance with all label, Worker Protection Standard (WPS) and state (e.g., California) regulatory requirements." So the stated intention is for the AHETF to only monitor and be aware of practices that are in accord with the label, WPS and state regulatory requirements.

Reviewing the completed study identifies a number of lessons, one of which is the value of determining actual use practices in the field prior to conducting the study. Neither EPA nor the AHETF anticipated the need to do this, and the protocol did not require it. Once the best practices directions for using water-soluble packets were adopted, in subsequent monitoring units, the AHETF applied the information in the field and implemented the amendments reflecting the best practices. Pages 19-20 of EPA's ethics review documents this.

The revised directions for using water-soluble packets were identified and brought to EPA's attention as a result of study AHE120. For EPA to rely on these recommended procedures, or even a revised version, EPA must comply with 40 CFR Section 26.1604 and submit the study and scenario monograph report to the HSRB for review. From an ethics perspective, to help promote the effectiveness of any revised procedures for the proper use of water-soluble packets, the procedures must be incorporated into required label language and replace any inconsistent label language, and the procedures must be followed. To increase the likelihood that the appropriate procedures and label language will be followed, agricultural handlers using water-soluble packets must be trained on the appropriate procedures. In summary, to achieve the intended benefits from the revised procedures, the appropriate, updated procedures should be incorporated into required label language for water-soluble packets; any conflicting language should be removed from the same labels; and agricultural handlers who are, or will be, using water-soluble packets must receive effective and timely training on the updated procedures.

In follow-up, EPA will pursue appropriate required label revisions identifying the proper use of water-soluble packets, as well as associated training for agricultural handlers using those water-soluble packets. In the process of doing this, EPA will consult with various stakeholders, such as the State FIFRA Issues Research and Evaluation Group, on the most effective approaches for ensuring that the updated procedures for the proper use of water-soluble packets actually reach the regulated community and influence their behavior when using water-soluble packets.

In summary, Ms. Lydon stated that the monitoring units and data on the unacceptable work practices are being used by EPA to pursue label amendments and associated training for handlers to help ensure that water-soluble packaging is used properly, thereby reducing exposure. EPA wants to pursue

those changes. To do so, EPA must rely on study AHE120. The AHETF, EPA and the HSRB previously agreed that a total of 25 mixers/loaders would be anticipated for this study. The AHETF did not consider going beyond the 25 monitoring units because exposing additional human subjects beyond the number agreed to by EPA and the HSRB could have been considered unethical, particularly because such exposure of additional subjects would not have been approved in advance by EPA, the HSRB or the IRB. EPA proposes to use the data from the unacceptable work practices in pursuing label changes and training, so the exposure of the associated subjects would actually result in regulatory action, assuming that EPA can rely on the study.

Regarding the review of use directions with subjects, EPA noted that neither the protocol nor the consent form requires that the use directions for the surrogate chemicals be reviewed with participating subjects. The study sponsor accurately pointed out to EPA that "Directions for Use" covers many topics not relevant to the study. Despite this, the AHETF covered with subjects the "Mixing Instructions" and "Mixing Order" information under the "Directions for Use" prior to mixing/loading. The workers were then generally allowed to perform their tasks using their normal procedures and application rates. As the water-soluble packets best practices were developed, the Study Director discussed them with the participants.

For the remaining agricultural handler exposure studies underway in the field, for those monitoring units not yet initiated, EPA has asked the AHETF, beginning in August 2016, to direct the Study Directors and/or their designees to review with participating subjects the pertinent sections of the "Directions for Use" on the label that are applicable to each study, and the AHETF has agreed to this.

Focusing on the personal exposure results for subjects, Page 7 of the consent form refers to the form that subjects use to request their personal study results. SOP 11.J.4 explains how the personal study data should be summarized for interested subjects; 16 of the 25 monitored subjects requested their personal results. The AHETF confirmed that personal exposure study data were provided to all of the interested monitoring units conforming to the best practice instructions. Eight of the nine monitoring units whose work practices were excluded from the study requested their personal results. The subjects whose work practices were unacceptable were given the mean results for the conforming subjects, along with the list of best practice instructions.

In addition to these end-of-study letters, workers M1 and M2 received initial notification letters, shortly after the exposure results were available, that essentially told them that their exposures were higher than expected, but the letters did not provide quantitative results or explain the distribution of the residues on their bodies, as outlined and required in the SOP.

In response to EPA's questions about why the personal results were not provided to these subjects, the AHETF explained that the samples from three of the monitoring units were not analyzed. For the monitoring units with higher than expected exposure, the AHETF did not think the results would reflect what their exposure would be when using best practices and would not be comparable to the mean results from the conforming monitoring units. For the monitoring units that had results in the range of the conforming MUs, AHETF wanted to send them their best practice instructions as an encouragement to adopt them. AHETF believed that providing them with results similar to the mean of the conforming monitoring units would not necessarily be an incentive for them to change their way of handling water-soluble packets. In all cases, AHETF provided the mean results across all conforming MUs and a copy of the best practice instructions. The monitoring units who requested personal results, but whose samples were not analyzed, were M16 and 17. EPA thinks that the personal exposure data in existence should have been sent to each of the subjects who requested his personal data, which would have been consistent with the protocol, consent form and SOP 11.J.4. The instances in which samples were analyzed but the personal results were not provided to the workers who requested them constitute a protocol deviation that

should have been reported to the IRB. EPA agrees that it was appropriate to share the updated procedures for proper handling of water-soluble packets; the workers' personal exposure data should have been provided, however, along with a comparison to the results for other workers performing the same task. EPA requested that the study sponsor provide the personal exposure data to every worker who requested but did not receive it, consistent with the signed informed consent forms, protocol and SOP. EPA advised that the results should be provided in a way that is comprehensible, relevant, contextualized and usable to those who requested information. The AHETF agreed to send the existing personal results to the six remaining workers, and the Task Force already has done so; therefore, the study sponsor has remedied this deviation from the protocol.

Regarding heat index monitoring, the heat index did not reach 105 degrees Fahrenheit during any of the monitoring sessions, and none of the monitoring units had to be terminated because of heat index. SOP 11.G.5 was followed, with one exception. The Study Director was supposed to inform all study observers at the start of the study of the current Heat Index Category, and the observer was supposed to be informed if or when the Heat Index Category subsequently changed. In practice, the observer started weather monitoring at the first opportunity after observing the first mixing/loading or when it felt warm enough to merit it. This is a protocol deviation. As follow-up in future studies, the study sponsor has agreed to pay close attention to and follow this aspect of the SOP.

Ms. Lydon then discussed protocol amendments. The protocol was amended 15 times, and the IRB approved these amendments prior to implementation. EPA's ethics review discussed specific components of Amendments 2, 3, 6 through 9 and 13, given their potential effect on ethical considerations. EPA disagreed with Amendment 9, which discontinued reviewing the Material Safety Data Sheets (MSDS) with subjects. The researchers confirmed, however, that they still reviewed with subjects the specific risks associated with the end-use product being handled, precautionary statements that should be followed, the requirement to use label-specified PPE, the importance of washing hands prior to eating or smoking, and other safe pesticide handling practices that should be followed.

The study sponsor also still required the medical professional who was onsite to review the safety data sheet before the monitoring event began and to have the sheet on hand during monitoring. As a follow-up action, the AHETF has agreed to reinstitute the review of the safety data sheet with monitoring units not yet initiated in their other studies, consistent with those study protocols.

EPA also noted that 11 amendments already had desired effective dates on them when they were submitted for IRB review, although they had not been implemented. OPP has emphasized to the study sponsor that the effective date or implementation date for a protocol amendment can never be prior to the IRB approval date unless a subject is facing an imminent hazard. As a follow-up action, when requesting IRB approval of an amendment, EPA requests that the study sponsor insert "IRB approval date" as the effective date. The study sponsor agreed. Unless an immediate or imminent hazard to a subject exists, the federal rule states that protocol amendments should not be implemented prior to IRB approval.

With regard to IRB oversight, the overseeing IRB reviewed and approved the initial protocol and 15 amendments. The AHETF submitted a reportable event to the IRB. The study sponsor did not identify or report any deviations. EPA identified two unreported deviations, and EPA addressed them in follow-up actions to which the study sponsor has agreed.

Regarding documentation, the AHETF satisfied the requirements of 40 CFR Section 26.1303. EPA identified six follow-up actions for AHETF and one follow-up action for EPA as a result of study AHE120. EPA is of the opinion that Study AHE120 met the substantive acceptance standards under 40 CFR Sections 26.1703 and 26.1705, as well as the obligations of FIFRA Section 12(a)(2)(P). EPA found that all subjects were at least 18 years of age and male. Pregnant or nursing women were excluded as required. No significant deficiencies in the ethical conduct of the research existed that would prevent EPA

reliance on the study. EPA identified follow-up actions for both the study sponsor and the Agency. The protocol was implemented as amended. EPA identified two unreported deviations, which are addressed in follow-up actions. The subjects were fully informed, and their consent was fully voluntary, without coercion or undue influence. Ms. Lydon concluded that the available information indicates that AHE120 was conducted in substantial compliance with Subparts K and L of 40 CFR Part 26.

Board Questions of Clarification—Ethics

Dr. Kyle Galbraith, HSRB member, asked whether the monitoring units whose monitoring was not completed were informed that their results were unavailable. Dr. Douglas Baugher, Study Director, stated that to the best of his recollection, if these individuals requested their results, they were informed that their results were unavailable and were provided with a description of best practices.

Dr. Dawson noted that exposure was five to 10 times higher for workers mixing/loading wettable powders than for workers using water-soluble packets. She asked whether EPA had informed workers or employers using wettable powders about the option of water-soluble packets after receiving the results of the two studies. Ms. Lydon responded that EPA did not plan such follow-up with workers or employers. Mr. Crowley added that some active ingredients might not be available in water-soluble packets. He speculated that the fact that a particular active ingredient is produced in water-soluble packets might be a result of an EPA determination that handling a particular chemical is particularly risky to workers' health. Dr. Dawson responded that employers might decide to select a particular active ingredient based on worker safety concerns, but she acknowledged that such an ethical consideration is beyond the Board's purview.

Public Comments

Mr. Downing indicated that no requests had been received by EPA in advance of the meeting to provide public comments. Dr. Dawson asked members of the public participating via teleconference to provide comments. Hearing no response, Dr. Dawson invited Dr. Ramos to present his scientific review.

Board Discussion—Science

Dr. Ramos stated that in his opinion, AHE120, like AHE80, was well crafted, designed and conducted. Many of the points made in the scientific review of AHE80 also apply to AHE120.

Dr. Ramos read the following first science charge question to the Board into the record:

> Was the research reported in the Agricultural Handler Exposure Task Force (AHETF) completed monograph report and associated field study report for AHE120 faithful to the design and objectives of the protocol?

Dr. Ramos responded that yes, the reported research for AH120 was faithful to the design and objectives of the protocol as amended and that the amendments were implemented throughout the course of the study.

Dr. Ramos read the following second science charge question to the Board into the record:

> Did the research generate scientifically reliable data, useful for assessing the exposure of individuals who mix and load conventional pesticides formulated in water-soluble packets?

Dr. Ramos responded that yes, the research generated scientifically reliable data, useful for assessing the exposure of individuals who mix and load conventional pesticides formulated in water-soluble packets, with similar limitations to those discussed during the previous day regarding AHE80 regarding the diversity of scenarios and uncertainty in exposure estimates.

Dr. Ramos noted that the completed reports did not address the issue raised during the HSRB's protocol review regarding calculating the time on task versus the total monitoring time.

Dr. Ramos also expressed concern regarding potential conflicts between using nonrandom and conventional statistical methods but deferred to Dr. Jun Zhu, HSRB member, on this issue.

Dr. Zhu presented her statistical review. She concurred with Dr. Ramos' responses to each of the two science charge questions. Regarding the relevance of the statistical methodology used given the nonrandom study design, Dr. Zhu stated that an analysis had been performed that compared treating the data independently with an analysis that accounted for a clustered sampling approach. This analysis had been thorough and adequate.

Dr. Gbur concurred with Dr. Zhu's assessment. He recognized that random sampling is preferable, but the realities of meeting recruitment goals must be acknowledged. Dr. Dawson noted that employers, rather than individual workers, had been reluctant to respond to invitations to participate in the study.

The participants discussed the time on task versus total monitoring time calculation. Dr. Maddalena noted that the monitoring data were normalized to the amount of active ingredient handled. Dr. Ramos expressed concern that the inherent variability of the measurements might have been affected by the time on task, especially when results were close to the detection limit. Mr. Crowley stated that EPA's review noted that the issue of time on task was not addressed explicitly in the research report. Field observations were made, however, that could be used to determine the time spent on different activities during monitoring. He added that the protocol requirement of monitoring worker exposure for at least 4 hours was removed to avoid monitoring results below the detection limit. The Board's original comment was made in the context of the 4-hour minimum sampling time. Additional requirements (e.g., minimum number of tank loads) were included that were more relevant to estimating exposure.

Dr. Dawson noted that in AHE120, establishing the proportionality of the data to AaiH was less difficult than for AHE80. Dr. Ramos replied that this was the reason he had cited only the limitations of limited diversity in scenarios and uncertainty in estimates of inhalation exposures, not failure to confirm proportionality of exposure with AaiH. Dr. Zhu concurred with Dr. Ramos, noting that the data in AHE120 were "better behaved" than those in AHE80. Dr. Dawson commented that perhaps the exposures' being lower and less variable was due to the effectiveness of water-soluble packets as an engineering control.

Dr. Ramos read the following proposed responses to the two science charge questions into the record:

- The research reported was faithful to the design and objectives of the revised protocol as amended.

- The study generated scientifically reliable data that may be useful for assessing exposures of individuals who mix and load conventional pesticides formulated in water-soluble packets, subject to limitations as noted in the report.

Dr. Ramos specified that the limitations refer to diversity of scenarios and the uncertainty of estimates for inhalation exposure. The Board members agreed unanimously to the responses.

Board Discussion—Ethics

Dr. Galbraith read the following ethics charge question into the record:

> Does the available information support a determination that the research was conducted in substantial compliance with 40 CFR Part 26, Subparts K and L?

Dr. Galbraith stated that the protocol was discussed in 2010 by the HSRB and approved by an IRB in 2010. At the time of review, the IRB was fully accredited. Protocol amendments were reviewed, and they were not implemented in the study until approved by the IRB. The consent was translated into Spanish. The greatest risk to participants was heat-related illness. A stopping procedure for heat-related illness was in place, but no heat risk was observed. All participants received training. One event was reported, which was reviewed by the IRB. Minors and lactating women were excluded from the study. A pregnancy test protocol was developed, but no women enrolled in the study.

In drafting his review, Dr. Galbraith had three minor concerns, but these were addressed by information provided during the previous day's meeting. The concerns were the following: (1) Only males participated in the study; (2) Only 16 of the 25 monitoring units' results were included in the analysis; and (3) Nonconforming monitoring units whose data were excluded and who requested their results did not receive them. Regarding the first concern, exclusion of females was not intentional, but few females are involved in the scenario. Regarding the second concern, Dr. Galbraith was more comfortable with the exclusion and its acknowledgment by the Task Force. Regarding the third concern, the Task Force is in the process of notifying the relevant monitoring units that their results are not available.

Dr. Galbraith read the following proposed response to the ethics charge question into the record:

> The available information support a determination that the research was conducted in substantial compliance with 40 CFR Part 26, Subparts K and L. The Board members agreed unanimously to the response.

Adjournment

Mr. Downing announced that the next HSRB meeting is scheduled for August 25, 2016, to finalize the Board's report from this meeting. This meeting will be held virtually. An additional meeting of the HSRB, which will be virtual as well, is scheduled for October 18–20, 2016. An additional day, October 18, was added because additional items need to be included on the agenda. Mr. Downing asked Board members to contact him if they are unable to attend on October 18. The October meeting likely will be scheduled during the afternoons of the 3 days, but notification of the final schedule will be posted on the HSRB website[3] and published in the *Federal Register.*

Mr. Downing commented that the virtual meetings were proceeding increasingly smoothly as the Board members become more accustomed to the format.

[3] The HSRB website is available at www.epa.gov/osa/human-studies-review-board.

Dr. Dawson requested that Board members who have updates to their written comments on the studies discussed in this meeting submit them to her via email by July 20 to ensure that the Board's final report accurately reflects its deliberations.

Mr. Downing adjourned the meeting at 4:02 p.m. EDT.

Respectfully submitted:

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

Certified to be true by:

Liza Dawson, Ph.D.
Chair
Human Studies Review Board
United States Environmental Protection Agency

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

Attachment A

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