Minutes of the
United States Environmental Protection Agency (EPA)
Human Studies Review Board (HSRB)
November 5, 2014 Public Meeting
Docket Number: EPA–HQ–ORD–2014–0750
HSRB Website: http://www.epa.gov/osa/hsrb

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

Date and Time:	Wednesday, November 5, 2014, 10:00 a.m. – 3:00 p.m. EST (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:	Rebecca T. Parkin, Ph.D., M.P.H.
	Vice Chair:	Jewell H. Halanych, M.D., M.Sc.
	Board Members:	Gary L. Chadwick, Pharm.D., M.P.H., C.I.P. Liza Dawson, Ph.D. George C.J. Fernandez, Ph.D. Kyle L. Galbraith, Ph.D. Edward Gbur, Jr., Ph.D. Elizabeth Heitman, Ph.D. John C. Kissel, Ph.D. Randy Maddalena, Ph.D. William J. Popendorf, Ph.D. Kenneth Ramos, M.D., Ph.D., Pharm.B. Suzanne M. Rivera, Ph.D., M.S.W. Jun Zhu, Ph.D.
Meeting Summary:	Meeting discussions generally followed the issues and general timing as presented in the Meeting Agenda (see Attachment C), unless noted otherwise.	

Wednesday, November 5, 2014

Commencement of Public Meeting and Review of Administrative Procedures

Before the meeting was called to order, there was a brief discussion and explanation of how to use the Adobe® Connect webinar system to accomplish the objectives of the meeting. Mr. Jim Downing (Designated Federal Officer [DFO], HSRB [or Board], Office of the Science Advisor [OSA], EPA [or Agency]) convened the meeting at 10:10 a.m. and welcomed Board members, EPA colleagues and members of the public. He expressed appreciation on behalf of the Agency for the time and diligent work of the Board members in preparing for meeting deliberations. He also thanked the EPA staff 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 requirements are met regarding the operations of the HSRB. Also in his role as DFO, he must work with appropriate Agency officials to ensure that all appropriate ethics regulations are satisfied. HSRB members were briefed on federal conflict of interest laws and have completed a standard government financial disclosure report, which has been reviewed to ensure that all ethics requirements are met.

Mr. Downing welcomed three new members—Drs. Gary Chadwick, Suzanne Rivera, and Jun Zhu—to the HSRB. He then introduced each of the new members:

- **Dr. Gary Chadwick** holds an Emeritus faculty appointment at the University of Rochester's School of Medicine and Dentistry as Professor of Medical Humanities and Bioethics. He retired after 16 years from his position as Associate Provost and Director of the Office for Human Subject Protection. He is currently a Senior Consultant at HRP Consulting Group, Inc., and focuses on accreditation, human subjects protection program evaluation, and training.

- **Dr. Suzanne Rivera** is the Vice President of Research and Technology Management at Case Western Reserve University. She has broad responsibility for oversight of the research enterprise, including development of research policy, pre- and post-award management of sponsored projects, scientific integrity, compliance with research regulations, and education of faculty and students regarding the responsible conduct of research. Since arriving at Case Western Reserve University, Dr. Rivera has implemented numerous research support initiatives, including the selection and roll-out of a new pre-award proposal management system and the development of an export controls program. Dr. Rivera also is an Assistant Professor in the Department of Bioethics, where she teaches research ethics to graduate and medical students. She is the Principal Investigator on a grant from the National Human Genome Research Institute, and she has published numerous articles and book chapters about research ethics and public policy.

- **Dr. Jun Zhu** is a Professor of Statistics with a joint appointment in the Department of Entomology at the University of Wisconsin, Madison. Dr. Zhu routinely teaches and provides statistical consultation on statistical methods that encompass experimental design, linear and generalized linear models, and random and mixed-effects models. Her primary research interests are in environmental, spatial and spatiotemporal statistics with application to agriculture, biology, ecology and environmental sciences. She has successfully collaborated with researchers in a wide range of disciplines, including environmental health, forestry, landscape ecology and spatial demographics. She also has conducted statistical methodology research in a variety of areas of statistics, including resampling methods, spatiotemporal statistics and Bayesian hierarchical models, which are motivated by problems that arise in the course of scientific collaborations.

Mr. Downing informed Board members that two interesting and challenging topics will be discussed during the meeting. He noted that agenda times are approximate, and the group will strive to have adequate time for Agency presentations, public comments and the Board's thorough deliberations. He noted that the virtual format of the meeting might present some technological challenges, but the participants will work together to ensure a successful meeting.

All participants should mute their lines when not speaking and state their name before providing remarks to ensure accurate attribution. Copies of all meeting materials will be available at http://www.regulations.gov under docket number EPA–HQ–ORD–2014–0750, and supporting documents are available on the HSRB website at http://www.epa.gov/osa/hsrb. Following the presentations, time has been scheduled for the Board to direct questions of clarification to EPA staff and the sponsors of the studies discussed. This time is to be used for points of clarification rather than Board discussion. There will be a public comment period, and remarks must be limited to 5 minutes. Mr. Downing noted that no individuals preregistered to provide public comments.

In accordance with FACA, meeting minutes, including a description of the matters discussed and conclusions reached by the Board, will be prepared and must be certified by the meeting Chair within 90 days. The approved minutes will be available at http://www.regulations.gov and on the HSRB website at http://www.epa.gov/osa/hsrb. The HSRB also will prepare a final report in response to questions posed by the Agency, which will include the Board's review and analysis of materials presented. The final report will be available at http://www.regulations.gov and on the HSRB website at http://www.epa.gov/osa/hsrb. Mr. Downing then turned the meeting over to the HSRB Chair, Dr. Rebecca Parkin.

Introduction of Board Members

Dr. Parkin welcomed the Board members and asked them to introduce themselves with names, affiliations and expertise. The Board members completed their introductions.

Welcoming Remarks

EPA Human Subjects Research Review Official (HSRRO) Dr. Toby Schonfeld (OSA, EPA) provided opening remarks. Dr. Schonfeld welcomed the Board members on behalf of EPA and expressed appreciation for their attendance. She reiterated the importance of the Board's work and asked for patience as any technical challenges are addressed during the virtual meeting. Dr. Parkin thanked Dr. Schonfeld for her comments.

Session 1: A new scenario design and associated protocol from the Agricultural Handler Exposure Task Force, LLC (AHETF) describing proposed research to monitor dermal and inhalation exposure of pesticide handlers who manually open containers of granular pesticide products and perform open-pour loading of the granules into application equipment

Background

Dr. Parkin introduced Session 1 and asked Mr. Jeff Evans (Office of Pesticide Programs [OPP], EPA) to present EPA's science review.

EPA Science Assessment

Mr. Evans described the open-loading scenario to be performed by the AHETF. The scenario involves the exposure of individuals loading granules into various machine-driven application equipment (primarily planting equipment). Product packaging will include any size up to 50 pounds that can be lifted easily by the participant; super sack containers and loose bulk

products will be excluded. The granules will be standard size that can pass through 4 mesh screens but be retained by 80 mesh screens. Only classic granules will be loaded, not engineered reduced-dust granular formations.

Activities involved include opening the product bags, pouring the granules into equipment, and moving full bags from storage or delivery vehicles. Subjects also will manage empty bags for disposal, prepare for the next load, and clean the application equipment. The AHETF will retain the empty bags. All activities performed by volunteers will be noted by observers. Because there may be downtime between loading events, other activities might include paperwork, equipment repair, or other activities that do not require the volunteer to come into contact with equipment contaminated with the surrogate.

The clothing scenario includes long-sleeved shirts, long pants, shoes and socks. Personal protective equipment (PPE) required for all volunteers will consist of chemical-resistant gloves. Participants also may choose to wear baseball style hats, glasses, protective eyewear and respirators, although aprons and face shields may not be worn. Mr. Evans noted that a standard operating procedure (SOP) will be used to extrapolate the measured face and neck wipe residues to the rest of the head to account for the additional attire or PPE worn by the participant.

Monitoring areas (MAs) are geographically distributed across the United States in seven regions. Within each MA, three individuals will be monitored, and a variety of crops will be included in the scenario. Typical exposure monitoring methods will be used for the scenario. Dermal exposure will be measured through a hand wash, face/neck wipe, and whole-body dosimeter (WBD) separated into upper and lower sections. Inhalation exposure will be measured with an air pump or Occupational Safety and Health Administration (OSHA) Versatile Sampler (OVS) tube.

Available for monitoring by the AHETF are 10 potential surrogate pesticides. Mr. Evans noted that volunteers handling the insecticide chlorpyrifos will satisfy the requirement for wearing a double layer through the WBD in addition to a single layer of clothing. Surrogate pesticides include a wide range of application rates to fulfill amount of active ingredient handled (AaiH) strata of 5–15 pounds (lbs), 15–150 lbs, and 150–400 lbs. The maximum amount is based on risk assessment assumptions of an application rate of 2 lbs active ingredient per acre and 200 acres treated per day. The individuals within each MA will handle different amounts of active ingredient, use different surrogates and load a variety of equipment to diversify the monitoring events and help achieve proportionality. The scenario will apply similarity restrictions per monitoring cluster. The AHETF requires that the monitoring units (MUs) within a cluster not be the same worker or have the same employer and prefers that the MUs not be within the same AaiH stratum.

Mr. Evans explained that all dermal and inhalation margins of exposure (MOE) are acceptable based on available surrogate handler exposure data, maximum active ingredient handled per day and current EPA toxicity endpoints and doses. He noted that chlorpyrifos currently is being re-evaluated, and the revised risk assessment is scheduled to be released in December 2014. EPA will re-evaluate the MOEs after the revised risk assessment is finalized. If the MOEs fall below acceptable levels based on the new assessment, EPA will immediately inform the AHETF of necessary changes to the protocol.

In closing, Mr. Evans stated that the open loading of granules into large-scale application equipment is a discrete task assessed at EPA and other regulatory entities. The scenario is straightforward. It does not involve the use of products engineered to reduce dustiness or address the use of any PPE other than gloves. Mr. Evans presented the conclusions of EPA's science assessment: The scenario is well defined, and the study is likely to produce reliable open-pour granule loader data to assess the potential exposure of handlers open pouring granular products.

Board Questions of Clarification—Science

Dr. Parkin invited Board members to ask questions for clarification. In response to a question from Dr. Randy Maddalena, Mr. Evans clarified that chemical-resistant gloves would be provided to the volunteers. Dr. Maddalena referred to the list of 10 active ingredients that will be used as surrogates for exposure to granules and asked whether individual active ingredients will be tracked in the study. Mr. Evans explained that active ingredients will be measured as an indication of exposure to granules. After the dermal and inhalation exposure per AaiH is defined in the study, those values can be extrapolated to the specific active ingredient during a risk assessment. Dr. Maddalena questioned whether the percent of active ingredient in a formulation was chemical-specific, thus affecting both measured transport efficiency and stratum distribution. Mr. Evans acknowledged that the strata of specific surrogates is difficult to predict, which formed the basis for the wide variety of active ingredients available for the study.

Dr. William Popendorf questioned the rationale for dividing the WBD into two sections versus six sections, as had been standard for previous studies. Mr. Evans replied that six sections are appropriate with scenarios that have high exposure levels, such as enclosed transfer systems. He explained that two sections will be useful for the Agency's purposes, and EPA acknowledged and accepted the limitation.

Dr. Popendorf asked about provisions for volunteers who might reach the MOE limit of 400 lbs. Mr. Evans explained that tasks would be limited for volunteers who would exceed the MOE in the course of their work for the day. Dr. Popendorf requested that those provisions be described in the study protocol.

Dr. Popendorf asked for clarification about the reference to "traditional" recruitment methods. Mr. Evans replied that traditional recruitment comprises personal references from previous volunteers, Cooperative Extension Service personnel and so forth. For this protocol, traditional recruitment methods will be utilized after the original randomized list of potential volunteers is exhausted. Dr. Edward Gbur, Jr., asserted that traditional recruitment methods do not lead to any randomization. He questioned whether the AHETF anticipated difficulty in recruiting volunteers for the study. Mr. Evans confirmed that recruitment is difficult. The study is involved, and workers are busy during the growing season. During randomized recruitment, thousands of people are called before finding five to 10 who are interested in participating. Recruitment efforts for the study include telephone calls, questionnaires, flyers, and information sources. Mr. Evans reminded the HSRB members that the Board previously had requested the inclusion of randomized elements in study protocols, and randomized recruitment was one way to achieve that goal. Dr. Gbur noted, however, that the potential reliance on traditional recruitment methods to supplement randomized recruitment efforts means that the sample might not be randomly selected. He expressed concern that the protocol is disruptive to the point that securing volunteers is difficult.

In response to a question from Dr. John Kissel, Mr. Evans asserted that individual data and time points from multiple hand-washing events recorded throughout the day for each volunteer will be aggregated in the report. Dr. Kissel emphasized that associating time points with the hand-wash data will allow analysis of temporal patterns. He also pointed out that in the MOE calculations, in some cases fractional absorption efficiency is applied, but in others the information is not available. Mr. Evans noted that EPA applies specific fractional absorption values for risk assessments. EPA's Health Effects Division is investigating fractional absorption properties and will take action accordingly on any changes that might affect the risk assessment process. Dr. Kissel asked about the saturation state of the granules, which could affect the bioavailability of the compound. Mr. Evans replied that the granules used contain the standard formulation of chemicals, and he was not aware of product chemistry requirements for these products. Dr. Maddalena clarified that the study is designed to measure the amount of active ingredient that contacts the surface of the individual, PPE or clothing; there is no indication for how much active ingredient is absorbed.

Dr. Parkin, noting no further questions of clarification, asked Ms. Kelly Sherman (OPP, EPA) to present her ethics review.

EPA Ethics Assessment

Ms. Sherman stated that the goal of the study was to develop better exposure data for a wide range of pesticides, data that can be used to support EPA risk assessments, indicating value to society. She described subject selection during the recruitment process. Eligible growers will be identified and must sign a non-coercion statement to indicate that they will not coerce their employees, either to participate or to not participate. After permission is granted to approach employees of eligible growers, subjects will be recruited through direct approach or distribution of flyers. The study will aim to recruit employees who perform open-pour loading of granular pesticides during their normal work. Subjects must have relevant open-pour experience within the last 3 years and must meet the other eligibility criteria to participate. Recruitment meetings will be held with prospective subjects, without employers or supervisors present, to explain the program, study, procedures, risks and benefits.

Detailed consent SOPs are provided with the study protocol. A private consent meeting will occur between the individual and a researcher. Bilingual investigators will ensure equivalent processes for Spanish and English speakers. The consent form contains all elements required by 40 Code of Federal Regulations (CFR) 26.1116. Ms. Sherman stated that the organization and presentation of risk information in the consent forms is thorough and acceptable. Ms. Sherman explained that risks were detailed in the protocol and consent form. The protocol provides appropriate measures to minimize each of the five categories of risk: heat-related illness, exposure to surrogates, exposure to surfactants, scripting of field activities and psychological risks. The most significant risk is heat-related illness due to wearing an extra layer of clothing. Two SOPs detail how the risk will be minimized through monitoring the heat index and the more sophisticated wet-bulb globe temperature (WBGT) index. The risk of exposure to surrogates and surfactants is minimized by including only self-identified healthy individuals. Regarding the scripting of field activities, the risks are minimized by selecting experienced subjects. Psychological risk will be limited by discreetly handling pregnancy test results and not including identifiable features in photographs and videos.

Ms. Sherman noted that although there is no direct benefit to subjects, sponsors will benefit from improved risk assessments that more accurately reflect actual exposure. The likely societal benefit is higher quality exposure and risk assessments for granular pesticides. Ms. Sherman stated that the risks have been fully identified and effectively minimized, are reasonable in light of potential societal benefits, and residual risks to subjects are low. The payments to subjects are reasonable, at $20 for consent and $80 for completion of the study. Subjects are free to withdraw at any time for any reason, and medical care for research-related injuries will be provided at no cost to the subjects. Procedures are in place to protect subject privacy.

The protocol and informed consent materials have been reviewed and approved by the independent Schulman Associates Institutional Review Board (SAIRB). The SAIRB's SOPs and membership roster are on file with EPA and have been provided to the HSRB members.

Given the proposal for third-party research involving intentional exposure of human subjects to a pesticide, with the intention of submitting the resulting data to EPA under pesticide laws, Ms. Sherman explained that the primary ethical standards applicable to the conduct of this research are 40 CFR 26, Subparts K and L, and Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) 12(a)(2)(P). EPA staff reviewed the study and concluded that the protocol meets the applicable ethical requirements of 40 CFR 26, Subparts K and L; no changes are recommended.

Ms. Sherman noted that AHETF is proposing the return of research results to study participants. Each subject will be provided the opportunity to request a summary of their personal results from the study. The results will include a comparison of results from other workers performing the same task. Ms. Sherman commented that this proposal to return research results is consistent with the majority opinion of the HSRB Work Group on the Return of Individual Research Results. She welcomed any thoughts or advice from Board members.

Board Questions of Clarification—Ethics

Dr. Parkin called for questions of clarification regarding EPA's ethics assessment. Dr. Elizabeth Heitman requested clarification about the recruitment process. Dr. Victor Cañez, study sponsor, replied on behalf of the AHETF. He described the multistep recruitment process, which will begin by identifying the names of crop growers using publicly available databases. That list will be randomized and called using a professional calling service to ascertain the application of one of the surrogate compounds, use of granules and application size of more than 10 acres. A researcher will then contact growers meeting the criteria to confirm eligibility. After the grower's eligibility and interest have been established, the study director will contact the individual and visit the facility.

In response to a question from Dr. Heitman, Mr. Evans noted that the AHETF used to recruit through local area coordinators and extension agents, rather than implementing the randomized process. Randomized recruitment was initiated in response to the Board's request to introduce as many random elements as possible into the process to remove real or imagined bias. Dr. Heitman noted that the randomized recruitment was complicated, but not unreasonable, and it might not be the most effective way of identifying subjects. Dr. Gbur countered that from a statistical perspective, one of the only methods to introduce randomization—and reduce the chance of bias—into the protocol is through subject selection. Dr. Heitman acknowledged the

point and noted that the rate-limiting step in most studies is recruitment, as individuals respond only when they have an interest in the study.

Dr. Chadwick requested clarification regarding the use of aprons and face shields. Mr. Evans explained that workers who use aprons and face shields would be ineligible to participate in the study.

In response to a question from Dr. Maddalena, Mr. Evans clarified that the researchers have the option to use either OVS or air pumps with filters depending on the selected surrogate.

Dr. Kyle Galbraith expressed concern that providing the pesticide granules for free to the growers might result in coercion of their workers to participate in the study. Ms. Sherman noted that the value of the chemical is small compared to the inconvenience of the study, and growers confirm that they will not coerce their employees. Dr. Liza Dawson stated that if risks are appropriately managed and the study is not dangerous to the participants, making the study attractive in compensation to an employer or participant is not an ethical issue. Monetary compensation becomes unethical if people are exposed to risk that they would otherwise not be willing to take. Dr. Dawson noted that the study is not very risky, and she suggested making the study more attractive to improve randomization. In response to a question from Dr. Gbur, Ms. Sherman explained that the subjects will be monitored at a place and time when they normally would be applying pesticides to crops. Dr. Gbur noted that this might interfere with a subject's usual work.

Dr. Parkin referred to Ms. Sherman's comment on the return of research results. She agreed that the proposed approach is partly in compliance with the HSRB work group recommendations, but some details are unclear. Ms. Sherman confirmed that individual research results, in the context of other subjects, would be presented to participants who opt in through the consent form. She noted that previous experience indicates that almost all study participants tend to request results. Dr. Parkin clarified that the work group had recommended that all subjects receive aggregate results and that those who want personal results opt in. She requested greater clarity in the protocol.

There being no additional questions about the ethics review, Dr. Parkin turned to Mr. Downing to call for public comments.

Public Comments

Mr. Downing announced that there were no public comments entered into the record. He called for any meeting participants to make a comment, and no public comments were offered by members of the public.

Charge Questions

Before beginning the Board's discussion, Dr. Parkin asked Ms. Sherman to read the charge questions into the record. Ms. Sherman read the following charge questions:

If the proposed research is revised as suggested in EPA's review and if the research is performed as described:

Charge to the Board—Science:

- Is the research likely to generate scientifically reliable data, useful for assessing the exposure of workers who perform open-pour loading of granular pesticides?

Charge to the Board—Ethics:

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

Board Science Assessment

Dr. Parkin asked Dr. Maddalena to provide his science assessment. Dr. Maddalena expressed appreciation for EPA's high-quality science review and the fact that the study was bounded on a specific exposure pathway. He began his review by discussing the scenario reports. There are four components to a loading scenario: formulation (granule), activity (pouring), packaging (bags) and equipment (receiving machinery). Each of the components is clearly defined, and the use of AaiH as a normalization factor is stated.

Regarding background and justification for the new work, Dr. Maddalena noted that the need for generic data has been described and confirmed through database review. The data provided by this scenario are expected to fill an important data gap for the open-pour granular scenario. The study is designed to coincide with naturally occurring workdays. Randomization is minimized, as the more important objective is to populate a data set with the full range of conditions. The idea is to create a set of MUs that span the range of AaiH and geographic conditions where open-pour loading is performed. Data analysis is limited, focusing on data quality and relative accuracy.

Dr. Maddalena then discussed the protocol document, which provides detail for each of the protocol steps and describes how the objectives will be satisfied. The protocol is based on EPA's guidance documents for dermal and inhalation exposure measurement under Series 875: "Occupational and Residential Exposure Test Guidelines." Dr. Maddalena asserted that the AHETF and contractors are qualified to perform the work. He acknowledged the need for balance between a desire for well-populated distribution of AaiH and the challenge of recruitment. Dr. Maddalena reiterated that the whole process was designed to capture the range of possible outcomes.

Regarding field materials and methods, the SOPs are very clear. Only experienced handlers are eligible, and scripting is performed as needed. In general, attempts will be made not to manipulate a subject's normal work. Dr. Maddalena expressed concern about the use of surrogates and the lack of differentiation between the available active ingredients. He did not find justification in the protocol document for the premise that all active ingredients are stable and will behave the same way from the bag to the exposure boundary. Dr. Maddalena also expressed concern about the use of OVS or air pumps with filters and suggested that both approaches be used in the protocol. Dermal exposure will be measured through the WBD to measure surface exposure. There are sufficient controls and quality assurance procedures,

although Dr. Maddalena expressed a preference for additional fortified samples to assess field recovery. He concluded his review by asserting that the study is thorough and complete, and should provide useful information to EPA.

Dr. Parkin requested that Dr. Maddalena direct any remaining questions to EPA. Dr. Maddalena asked whether the granule will provide a good surrogate in transferring particles to the handler. Mr. Evans confirmed that given the low vapor pressures of the pesticides, exposure to the active ingredient will be measured. The underlying premise for all of the studies is that the physical process of handling granules will affect exposure more than the properties of specific active ingredients. In response to another question from Dr. Maddalena, Mr. Evans explained that the subjects' dermal and inhalation exposure per AaiH factor will be applied in a risk assessment for other chemicals. In this way, the process is generalized to focus on the physical action and reduces the need to perform a separate study for each chemical. Dr. Maddalena acknowledged the need to generalize the studies. He reiterated his recommendation to measure inhalation exposure with both OVS and air pumps with filters to test the validity of the assumption that the active ingredient is staying on the particle long enough to reach the dosimeter. This would ensure that the surrogates are good indicators of transport. Dr. Maddalena also favored the use of biomarker measurements to capture exposure information on any particles that are absorbed by the body. A meeting participant remarked that WBDs are likely to overestimate exposures, so any error is in a protective direction.

Dr. Kissel noted the rule of thumb that the granules are composed of 10 percent active ingredient and likely to be saturated. Active ingredient at the surface of the granule is likely to behave like pure compound, transferring readily to the skin. Dr. Kissel noted that bare skin on the face and neck will absorb the compound, and washing might not be effective in removing the compound to measure for exposure.

Mr. Evans clarified that three controls will be used to correct for each MU. He also commented that EPA is studying wash data from dermal studies *in vitro* and *in vivo,* and the results are likely to inform future studies. In response to a question from Dr. Popendorf, Mr. Evans noted that separate scenarios will address wettable powders, open liquid, and closed systems.

Dr. Popendorf recommended that the HSRB develop a form of classification as an indicator of randomness to address the traditional versus randomized recruiting method. He also suggested that the Agency include an upper limit on each MU to prevent exposure to unacceptable MOE. Referring to Dr. Maddalena's suggestion to place the air pump filter upstream of the OVS tube to address concerns over vapor versus particle exposure, Dr. Popendorf agreed that placing the air pump filter in series with the OVS tube was a good idea. Dr. Maddalena elaborated that the quality of the surrogate as a marker of granule transport to the surface is dependent on how well the surrogate stays in place long enough to be measured. This is another way to demonstrate the assumption of stability.

Dr. Parkin asked Dr. Gbur to provide his comments. Dr. Gbur remarked that stratifying a large portion of the country into MAs and selecting MUs within each area is an acceptable approach for the study. The justification for selecting seven MAs and three MUs per area is reasonable given practical and cost constraints. The study design will take into account differences between regions, climates and crops. The inclusion of three MUs per area, however, results in only one MU within each AaiH stratum. Dr. Gbur expressed concern over the small

sample size, noting that the 95 percent confidence interval will be affected and that the entire range of conditions will not be adequately covered. He also was concerned about the lack of replications for the 21 individual observations. It is clear that the sampling design is solid, but the sample size is of concern, given the large range of conditions. Dr. Gbur expressed doubt that the data collected will be sufficient for a solid statistical analysis for some future purpose.

Mr. Evans thanked Dr. Gbur for the excellent point. If the AHETF is not confident in the results after collecting 21 MUs, Mr. Evans remarked that more MUs could be identified and monitored. In response to a question about the wide variety of classes of the available surrogates, Mr. Evans assured Dr. Gbur that similar study designs have produced successful results in the past. The data generated likely will be sufficient for practical conclusions.

Dr. Parkin announced a lunch break prior to the ethics assessment. She conducted a roll call to determine the members present on the teleconference following the lunch break.

Board Ethics Assessment

Dr. Parkin asked Dr. Dawson to provide her ethics review. Dr. Dawson stated that she did not identify any ethically problematic issues with the protocol. In her ethics assessment, Dr. Dawson assumed that the MOEs are valid estimates of a safe level of exposure. Regarding the first topic of risk to the subject, the protocol states that chemical exposures will be within the acceptable risk, unlikely to cause concern.

With regard to the idea of "minimal risk," Dr. Dawson explained that the protocol is not risky. Reviewers tend to use the term minimal risk if exposure differs from the background condition, but this does not mean that the risk is greater than general. Dr. Dawson took issue with the statement that wearing the WBD as an extra layer will increase the risk of heat-related illness because common sense dictates that the risk would not be greater than minimal. She emphasized the importance of ensuring that review of human subjects issues is scientifically realistic to retain credibility. There are precautions being taken, and the elevated risk is very small and reasonable. Dr. Dawson reiterated that the risks are acceptable and the precautions adequate. Additionally, the description of the precautions are detailed enough to ensure that the subjects will be monitored, reminded of safe handling procedures and given breaks if it becomes hot.

Regarding the selection of subjects, Dr. Dawson informed the Board members that employers are not allowed to pressure anyone to participate. Because this type of study is not inherently risky and does not deviate far from normal workday activities, she recommended compensating the subjects or employers to make the study more attractive and ensure scientifically robust results. The study inclusion criteria are reasonable, as English and Spanish speakers are accommodated. Given that some agricultural workers are low-literacy, the provisions to accommodate subjects who cannot read ensure fairness. Dr. Dawson approved the informed consent processes without supervisors present, as well as protections to subjects' privacy and confidentiality. She acknowledged that medical care, if necessary, would be provided at no cost to the participants. The protections seem reasonable for those economically disadvantaged. Overall, Dr. Dawson approved all of the procedures outlined in the protocol, recognizing that many of the SOPs already have been optimized by the AHETF.

Dr. Parkin opened the discussion to comments from the Board. Dr. Chadwick expressed concern about the scripting of field activities. Although scripting might increase exposure

through potentially longer periods of handling, he observed that a discussion of those risks was not present in the consent form.

Dr. Chadwick also questioned whether adequate protections were in place for undocumented workers. He expressed concern that inadequate protections of subjects' confidentiality would result in disclosure of information to local or state government agencies. Dr. Chadwick asked about any protections in place for accidental disclosure of personally identifiable information of undocumented persons. Dr. Dawson noted that although the study report will be provided to government agencies, the protocol explicitly states that names will not be disclosed, consistent with protecting confidentiality. Thinking the AHETF will take names and send them to Immigration is an unreasonable worry. Dr. Chadwick mentioned that he was concerned about the possibility of the AHETF losing the personally identifiable information accidentally. Dr. Dawson commented that the protocol states that a subject's name will appear only on the consent form; this type of study does not collect demographics or medical information. Dr. Dawson expressed concern about making the study sound more risky than it is by providing details about events that most likely will not occur. Dr. Heitman commented that any growers who employ undocumented workers are unlikely to agree to participate in the study. Undocumented workers, however, do tend to be a higher exposed population, so it is important to include them to the extent possible. Dr. Heitman also raised the issue of payments greater than $20 necessitating tax reporting, which would exclude undocumented workers. HSRB Vice Chair Dr. Jewell Halanych stated that in her experience, undocumented workers are unlikely to volunteer for activities where they must provide information.

Dr. Chadwick noted that providing payment always raises the issue of coercion, although $20 and $80 seem reasonable for a day's work. Dr. Parkin asked Dr. Chadwick to clarify whether he would like changes introduced into the consent form or protocol. Dr. Chadwick requested greater clarity with regard to the issues of undocumented workers introduced into the protocol.

Dr. Parkin asked Drs. Maddalena and Dawson to present the statements in response to the charge questions for voting by the Board. After a few minor modifications, the science charge question and response were read by Dr. Maddalena:

1. If the proposed research is revised as suggested in EPA's review and if the research is performed as described, is the research likely to generate scientifically reliable data, useful for assessing the exposure of workers who perform open-pour loading of granular pesticides?

   The Board concludes that given the clearly defined boundaries of the protocol, if performed as described and as recommended, the AHE170 protocol is likely to generate scientifically reliable data and will be useful for assessing the exposure of those who perform open-pour loading of granular pesticide products.

All of the Board members approved the response. Regarding the second charge question, Dr. Chadwick requested that the scripting risks be introduced into the consent form. Dr. Dawson disagreed, remarking that scripting does not increase the risk. She added that the AHETF went to great lengths to characterize actual risks, and there is danger in dramatizing activities that are not inherently risky. Furthermore, she noted that including more risks in the consent form will dilute subjects' ability to pay attention to the actual risks. Dr. Chadwick referred to page 64 of the

protocol, which described scripting as potentially increasing risk because the subjects' normal behavior would be changed. Dr. Parkin informed Dr. Chadwick that if the issue affected his opinion of whether the proposed research meets the ethical standards, then the HSRB consensus statement should be modified. Otherwise, the concern can be noted in the Board's report. Ms. Sherman identified a sentence in the consent form that indicates that the risks might be higher if the subject handles more active ingredient or works longer, which addresses the additional risk of scripting. Dr. Chadwick agreed that statement was acceptable.

Dr. Dawson read the ethics charge question and consensus statement for the Board's approval:

2. If the proposed research is revised as suggested in EPA's review and if the research is performed as described, is the research likely to meet the applicable requirements of 40 CFR Part 26, Subparts K and L?

   If the research is performed as described, it is likely to meet the applicable requirements of 40 CFR Part 26, Subparts K and L.

Dr. Parkin called for a vote, and the HSRB unanimously approved the statement.

Session 2: A published report by Frampton *et al.* (2002) of an intentional exposure human study measuring the effects of nitrogen dioxide exposure on airway and blood cells

Background

Dr. Parkin called Session 2 to order and introduced the topic before inviting LT Jonathan Leshin (OPP, EPA) to make his presentation describing EPA's science review.

EPA Science Assessment

LT Leshin explained that the study was conducted at the University of Rochester, and the purpose was to determine the health effects of nitrogen dioxide exposure, specifically addressing inflammation in the lung. Study subjects included nine females and 12 males, all of whom were lifetime nonsmokers with normal spirometry, free of cardiac or respiratory disease, and without symptoms of respiratory infection within 6 weeks of the study. Subjects were exposed to nitrogen dioxide gas at 0.6 parts per million (ppm) and 1.5 ppm in an air-controlled room. The study required four nonconsecutive days. Day 1 involved subject screening, informed consent and baseline measurements. Days 2, 3 and 4 involved exposure in a double-blind fashion to either air or one of the two nitrogen dioxide concentrations for 3 hours in an environmental chamber. Each participant was exposed to each condition, and each exposure was separated by 3 weeks from the previous exposure. The participants exercised for 10 minutes of each 30-minute interval at an intensity to increase the minute ventilation to 40 liters per minute. Physical, blood, cell typing and infection measurements were recorded for each subject.

LT Leshin described the study results. He noted that the effect of exposure to nitrogen dioxide varied by dose and gender. Nitrogen dioxide exposure reduced hematocrit, hemoglobin, red blood cell count and blood lymphocyte levels. Specifically, hematocrit was reduced by 4.1 percent. Results from bronchial lavage indicate that exposure to nitrogen dioxide increased polymophonuclear leukocytes. Lymphocyte levels also were increased following the bronchial

and alveolar lavage procedures, consistent with the idea that lymphocytes are entering the alveoli in response to irritation or injury. After cells from the lavage were exposed to influenza or respiratory syncytial virus, a trend toward increased cell death was observed, indicating that the cells are more sensitive to respiratory viruses following nitrogen dioxide exposure.

LT Leshin relayed the study conclusions: (1) Nitrogen dioxide decreases the red blood cell (RBC) number and hemoglobin concentration, which might be important in persons with cardio or pulmonary compromise, the elderly or children. (2) Nitrogen dioxide effects lymphocyte recovery from both blood and lavage fluid (decreasing in blood and increasing in lavage), suggesting that nitrogen dioxide increases recruitment of lymphocytes to the airways. (3) Nitrogen dioxide has an effect on lung cells, as seen by an increase in lactate dehydrogenase (LDH) release post viral exposure. (4) Nitrogen dioxide induces a variety of changes in the types and ratios of lymphocytes in the blood and lavage fluids, which might be differential to gender and likely indicates at least a mild inflammatory response. The lowest observed adverse effect level (LOAEL) was set at 0.6 ppm nitrogen dioxide. LT Leshin closed his presentation by reiterating that nitrogen dioxide produces a mild inflammatory response and the effect is related to gender.

Board Questions of Clarification

Dr. Parkin asked for questions of clarification. Dr. Popendorf observed that the authors did not discuss how nitrogen dioxide was measured in the exposure chamber. LT Leshin referred to the following passage from the Frampton article:

> NO_2 concentrations were generated by introducing NO_2 gas in air (5,000 ppm compressed gas; Air Products, Allentown, PA) in a Venturi mixer… Continuous monitoring of the residual background levels (ppb) of NO_x, ozone, particulate matter, and SO_x in the purified intake air was performed.

LT Leshin replied that the article stated an "achieved" concentration, suggesting that the levels had been measured. Dr. Popendorf disagreed with the conclusion.

Hearing no additional questions of clarification, Dr. Halanych asked Ms. Sherman to present EPA's ethics review.

EPA Ethics Assessment

Ms. Sherman informed the Board members that under EPA guidelines, the Frampton report is considered an intentional exposure toxicity study and therefore required to undergo review by the HSRB. She mentioned that the information for EPA's ethics review was based on information obtained from Dr. Mark Frampton. Ms. Sherman and LT Leshin sent a list of risk questions to Dr. Frampton, and his responses were provided to the HSRB members for review. The University of Rochester Institutional Review Board (IRB) provided a copy of the approval letter and consent form for the protocol.

Ms. Sherman outlined the ethical considerations for the study. Regarding subject selection, 21 subjects ages 18 to 40 years were selected for the study. The nine females were tested for pregnancy prior to each exposure session, and none were found to be pregnant. All subjects were recruited from the University of Rochester community and local population

through flyers. Subjects were limited to lifetime nonsmokers with normal spirometry, no cardiac or respiratory disease, and without symptoms of respiratory infection within 6 weeks of the study.

Interested subjects were initially screened by telephone, and the study was explained during an in-person meeting. The consent form explained the basic study procedures, risks and discomforts. Each subject provided written informed consent and was told that he or she could withdraw at any time. The consent form stated the possibility that subjects might experience airway irritation and coughing from the exposure. The consent form adequately explained the risk from the bronchoscopy procedure. Risks were minimized by enrolling only healthy subjects and closely monitoring the subjects during and after the procedure.

With regard to respect for subjects, the payment schedule was described as $50 each for the two initial exposures and $450 for the final exposure. Ms. Sherman noted that subjects' privacy was protected as indicated by procedures outlined on the consent form. The research was reviewed and approved by the Research Subjects Review Board of the University of Rochester to ensure ethics oversight.

Ms. Sherman described the ethical standards applied for the conduct of the study, which EPA must consider when determining reliance on a completed study that was conducted prior to implementation of the 2006 Human Studies Rule. EPA regulations governing the Agency's reliance on research contain two standards. Standard 40 CFR Section 26.1703 prohibits EPA reliance on data involving intentional exposure of pregnant or nursing women or of children, and Section 26.1704 prohibits EPA reliance on data if there is clear and convincing evidence that the conduct of the research was fundamentally unethical or was deficient relative to the ethical standards prevailing at the time the research was conducted in a way that placed participants at increased risk of harm or impaired their informed consent.

Ms. Sherman stated that the conclusion of her review was that the requirements of CFR Section 26.1703 were met by the study because the subjects were over age 18 and the females were tested for pregnancy. Regarding CFR Section 26.1704, there was no clear and convincing evidence that the conduct of the research was fundamentally unethical, and there was no clear and convincing evidence that the conduct of the research was deficient relative to prevailing ethical standards. There was no evidence of any intent to harm the subjects. The subjects were adequately informed, the study underwent an independent ethics review and approval, pregnant women were excluded, and subjects were monitored before and after the procedures in accordance with the ethical standards at the time. Ms. Sherman presented EPA's conclusion that if it is deemed scientifically valid and relevant, there are no barriers to EPA's relying on the study.

Board Questions of Clarification

Dr. Parkin asked for questions of clarification. In response to a question from Dr. Halanych, Ms. Sherman confirmed that all of the subjects completed the study without adverse events, and none withdrew from the study.

Public Comments

Mr. Downing called for public comments, and none were offered.

Charge Questions

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

Charge to the Board—Science:

- Is the Frampton *et al.* (2002) study scientifically sound, providing reliable data?
- If so, is this study adequate for quantitative use in support of an inhalation risk assessment for the use of nitrogen dioxide as a medical equipment sterilant?

Charge to the Board—Ethics:

- Does the study meet the applicable requirements of 40 CFR Part 26 Subpart Q?

Board Science Assessment

Dr. Parkin asked Dr. Popendorf to provide his science review. Dr. Popendorf remarked that what had initially appeared as a straightforward analysis now seemed more complicated. He opined that the biological sample collection and analytical methods comprise very good work, including the double-blind design and duplicate sample analysis. Dr. Popendorf described two concerns, specifically in regard to the operation of the exposure chamber and the statistical handling of outliers.

With regard to the chamber, Dr. Popendorf detailed four areas of concern. The authors state on page L156 that "For comfort, temperature and relative humidity were maintained at 37.1 ± 3.0°C and 21.2 ± 0.92% (mean ± SD), respectively." This temperature corresponds to 98.8°F, which is outside of the normal comfort range and poses a concern, especially when the temperature is combined with an exercise regime. No recognition of this risk is mentioned within the paper. Dr. Parkin commented that she also noticed the reference to 37°C and assumed that it was a typographical error.

The authors state "The capabilities for generating and maintaining pollutant levels and constant temperature and humidity have been described previously (48)." This citation is probably an error and should have been reference 49, where the design capabilities of this chamber are described: "This system [(S), (DX), (R) and (H)] was designed to vary the chamber temperature from about 10°C to 31.5°C and relative humidities from about 25 to 85%." These limits are repeated in the text and Table 1. Thus, the research seems to have been conducted outside of both the temperature and humidity range for which the chamber was designed. No comment regarding exceeding these limits was found within the paper.

Dr. Popendorf also raised an issue about the authors' claims in the article that are taken nearly verbatim from reference 49. One statement, referring to 0.3 atmospheric changes per minute, "enabled NO_2 levels to reach more than 90% of target levels within 4 minutes," is technically incorrect. Comments elsewhere in reference 49 read, "A volumetric control is incorporated into the chamber air supply to stabilize the air flow at 10 m^3/min" and "the effective chamber volume is approximately 40 m^3." The ideal air exchange time is 40 m^3 divided by 10 m^3/min, or the 4 minutes referred to by the authors. However, 2.3 air changes are needed to reach greater than 90 percent of target levels of nitrogen dioxide, which can take 9 minutes. The

authors do not describe how the exposure chamber was set up before the subject entered, so the length of time in advance that nitrogen dioxide was injected into the room cannot be ascertained. It is unclear whether this error had any substantive effect on the exposure conditions experienced by any test subject. This issue reflects the authors' deficient understanding of the operation of the chamber.

Dr. Popendorf noted that another claim is potentially of more concern. "The concentrations of NO_2 at the 3- and 6-ft levels within the chamber varied by no more than 5% of the mean." No method of measuring nitrogen dioxide was mentioned in the article, and this is not a trivial measurement. Dr. Popendorf acknowledged the possibility that the claim was copied from reference 49, which states "sampling of test aerosol concentrations at 3' and 6' levels (3 x 3 matrix) within the chamber has revealed that the aerosol concentrations vary by no more than ± 5% of the mean." A later paragraph in reference 49 elaborates that "Chamber monitoring is based on environmental factors, e.g. temperature, air flow, relative humidity, and the pollutant per se." This statement implies that the authors of Frampton *et al.* base their exposure values on the rate at which the compressed gas was introduced into the chamber. Thus, it is likely that the nitrogen dioxide concentrations were not measured within the exposure chamber and the authors might not have achieved the expected nitrogen dioxide concentrations. Dr. Popendorf remarked that based on his personal experience, measuring nitrogen dioxide is not an easy task because of its reactivity. He expressed concern that the authors neglected to discuss how the gas was measured, indicating that they might have had a limited understanding of how the chamber worked and the subjects' actual exposure.

Regarding the statistical concerns, Dr. Popendorf observed that the only time outliers are mentioned in the article is as a virtual afterthought to the last sentence in the METHODS section, which reads, "Data means shown in RESULTS include all study subjects, even though statistical outliers were excluded for the ANOVA." No additional details are provided. Dr. Popendorf mentioned another concern about the analysis, which centers around the details of the ANOVA used in conjunction with a three-period cross-over design and its equivalence to a paired *t*-test. He noted that statistical differences are more likely to be generated with a paired *t*-test.

Dr. Gbur provided his science review. He remarked that the study design was commonly used in this type of situation. The three-period crossover design was appropriate, and the delays between each session reasonable. The washout period helps to reduce carryover. Dr. Gbur expressed concern, however, that although a pre-study power analysis apparently indicated that four subjects for each of the six treatment sequences would provide adequate power, no details of the analysis were provided. Additional subjects were recruited to allow for dropouts, but only data from 21 subjects are reported in the paper, which does affect the power. The analysis variance was performed well, including period and crossover effects, and checks on model assumptions were completed. These standard procedures strengthen the acceptability of the results.

Dr. Gbur's main concern related to the outliers. The authors did not indicate which measurements had spurious data and how frequently they occurred. Removing outliers is an acceptable practice as long as it is reported as part of the methods, but the outliers were included in the bar chart results, which is concerning. Figure 4A is a good example of this issue, as the graph does not appear to support the authors' conclusions. Dr. Gbur identified similar issues with other figures in the article. He remarked that the numerical results likely are accurate, but

expressed concern about the conclusions based on the graphs. Aside from those issues, Dr. Gbur stated that the study design and analysis were statistically sound.

Dr. Parkin expressed appreciation to Drs. Popendorf and Gbur for their care in identifying the issues in the article. She mentioned that the Board could recommend that EPA query Dr. Frampton about several of the questions. If such an action is taken, Dr. Popendorf noted that more information about the nitrogen dioxide measurements would be particularly helpful. If nitrogen dioxide concentration was not measured in the chamber, the exposure results are incorrect, but if measurements were taken, Dr. Popendorf opined that the other concerns are peripheral, as the analysis does support the article's conclusions. LT Leshin stated that EPA would ask Dr. Frampton to clarify the nitrogen dioxide measurements and temperature reading. He noted that the article's results are consistent with other publications. Dr. Kissel observed that any responses would not be present in the peer-reviewed literature, which is unsatisfactory. LT Leshin commented that common practice in scientific publications is to perform experiments in a consistent way to a cited reference and, since both articles were generated by the same laboratory, it is likely that the measurements in the Frampton *et al.* (2002) article were consistent with reference 49.

In response to a question from Dr. Parkin, LT Leshin asserted that the Frampton *et al.* (2002) article was the most appropriate for the Agency's use related to occupational exposure situations. This particular article was the most relevant based on the number of relevant endpoints and length of exposure. LT Leshin elaborated that the Agency's concern was related to occupational exposure in a medical sterilization environment.

LT Leshin remarked that a 9-minute equilibration period to reach the desired nitrogen dioxide concentration would not have a significant effect given the 3-hour exposure window. Dr. Kissel reiterated the concern about the delivery of nitrogen dioxide at the expected concentrations.

Dr. Chadwick commented that the 37°C measurement might refer to the temperature of inspired air at a subject's mouth. Dr. Halanych asserted that was unlikely from a clinician's perspective. LT Leshin affirmed that EPA would consult Dr. Frampton about the questions. Dr. Heitman added that the University of Rochester research facility might be able to answer the questions about standard measurement practices if the principal investigator cannot.

Hearing no additional comments on the science assessment, Dr. Parkin then turned to the ethics review.

Board Ethics Assessment[1]

Dr. Parkin asked Dr. Heitman to present her ethics review. Dr. Heitman began by thanking Ms. Sherman and LT Leshin for their efforts to obtain additional information from the study investigators and the University of Rochester IRB. The information was very helpful, but Dr. Heitman cautioned that many IRBs do not keep such materials for long time periods, and this type of information might not always be available for future reviews.

[1] Editorial Note: At this point in the meeting, Dr. Chadwick recused himself. Therefore, he was not a voting member for this topic.

Dr. Heitman expressed great concern about the typographical errors in the paper. She was distressed by the potential scientific inaccuracy in a peer-reviewed article. Dr. Heitman asserted that no ethical questions were raised, and the article meets the applicable requirements of the 40 CFR Part 26 Subpart Q. Appropriate recruitment efforts were apparent, and no children or pregnant/nursing women were enrolled. Dr. Heitman noted that the information about pregnancy testing was obtained by Dr. Frampton after publication of the report. Additionally, the IRB review by the University of Rochester ensured that the study was consistent with the regulatory standards of 1996, including 45 CFR 46, and the ethical guidance of the Belmont Report.

Regarding the assessment of risks and benefits, Dr. Heitman noted that the article reports that many Americans are exposed to levels of nitrogen dioxide at the levels seen in the study, although one question was whether the subjects actually were exposed to those levels given the uncertainty of the chamber measurements. The risk was no greater than a minimal risk. Neither the article nor the consent form, however, addressed the balance between risk and benefit in the article. The University of Rochester IRB's approval of this study can be interpreted as its assessment that the risks to participants did not outweigh the study's anticipated benefits under ethical and regulatory standards in place at the time of its review. Dr. Heitman noted that because the bronchoscopy was not the primary risk, the risk of exposure to bronchoscopy might have been downplayed in the consent form.

Dr. Heitman continued, noting that the recruitment process was comprehensive, and subjects were provided an opportunity to ask questions. Vulnerable populations were not targeted, but as in many clinical studies, the study population might have been subject to coercion as students or staff of the University of Rochester. There was no statement that participants were not subject to interpersonal pressure. Dr. Heitman expressed a preference for paying subjects the full amount regardless of whether all exposures were completed. She noted that $50 for a bronchoscopy and blood draw was low, but approved by the IRB. Dr. Heitman stated that with exception to the concerns about the scientific measurements, there were no ethical questions as to the legitimacy of the study.

Dr. Halanych also expressed shock about the bronchoscopy procedure. At the time, it was standard to use conscious sedation for bronchoscopy. Atropine was used in the study, and clinical trials have not demonstrated a benefit of the use of atropine for bronchoscopy. Dr. Halanych acknowledged that her concern did not apply to 40 CFR, but she would not have signed up for the study. Dr. Heitman confirmed that bronchoscopy is not a safe procedure.

Dr. Parkin asked for other comments on ethics, and hearing none, she took a vote on the Board's responses to the scientific and ethical charge questions.

Dr. Popendorf read the Board's response to the first charge question: (1) The sample collection and laboratory analysis is scientifically sound. (2) The chamber exposure component might not be sound; more information is needed to assess actual exposure levels to nitrogen dioxide. (3) Statistical analysis is adequate to justify the significant differences that the author identified, but might not be adequate to detect all differences that might have occurred.

All of the Board members agreed with part 1 of Dr. Popendorf's response. Dr. Kissel disagreed with part 2, suggesting that the statement be phrased more assertively to note that barring additional information, the study does not adequately describe the exposure conditions. Dr. Popendorf modified the second part of the response to read, "The chamber exposure data are

not reliable without more information regarding actual exposure levels to nitrogen dioxide." Regarding the third point, Dr. Gbur remarked that reviewers of almost any study can identify additional analyses that should have been conducted. Dr. Popendorf clarified that the question under review by the Board is whether the statistics are adequate to address the Agency's intended use of the study. LT Leshin commented that the second charge question is predicated on the adequacy of the study for quantitative use in a risk assessment, and he suggested moving the third part of Dr. Popendorf's response to address the second charge question. All Board members agreed with the revised response to the first charge question:

1. Is the Frampton et al. (2002) study scientifically sound, providing reliable data?

   The sample collection and laboratory analysis are scientifically sound. The chamber exposure data are not reliable without more information regarding actual exposure levels to nitrogen dioxide.

Dr. Parkin restated the second charge question, and asked Dr. Popendorf to provide the Board's response. The Board members deliberated several issues, including replacing the term "semi-quantitative" in the response with the phrase "as part of a weight-of-evidence approach." In response to a question from Dr. Halanych, Mr. Tim Leighton (OPP, EPA) elaborated that the Agency is concerned with exposure to nitrogen dioxide during medical equipment sterilization. The closed sterilization system is exposed to 100 ppm nitrogen dioxide, and the concern is whether workers standing outside the sterilization chamber require respirators for safety. Dr. Parkin asked Dr. Popendorf to read the revised response to charge question 2 for voting:

2. If so, is this study adequate for quantitative use in support of an inhalation risk assessment for the use of nitrogen dioxide as a medical equipment sterilant?

   The statistical analysis is adequate to justify the significant differences that the authors identified, but was not adequate to detect all of the differences that may have occurred. This study may be used in a quantitative way as part of a weight-of-evidence analysis to support effects that might occur at the exposure levels reported, 0.6 and 1.5 ppm, but the study as published is not relevant to support the existence of no effects at the claimed levels of exposure.

All members approved the revised response to charge question 2. Dr. Parkin read the third charge question and asked Dr. Heitman to provide the Board's response:

3. Does the study meet the applicable requirements of 40 CFR Part 26 Subpart Q?

   The published report by Frampton et al. submitted for review meets the applicable requirements of 40 CFR Part 26 Subpart Q and the data within this article may be considered acceptable for EPA reliance contingent upon the determination of their scientific validity.

All Board members voted "yes" and the statement passed.

Closing Remarks

Dr. Parkin thanked the Board for the incredible meeting and expressed appreciation to all of the members for their time, effort, preparation and patience with the virtual meeting format. She turned the meeting over to Mr. Downing.

Mr. Downing also expressed appreciation for the Board members' participation and willingness to work within the virtual meeting format. He announced that the next HSRB meeting is scheduled for January 14–15, 2015, and the exact times will be posted in the *Federal Register*. Ms. Sherman stated that the meeting will address a completed AHETF study containing two separate scenarios on the treatment of rights-of-way with handheld sprayers and backpack equipment, as well as consider three journal articles related to fluoride. The meeting will likely be in-person because of the extensive agenda.

Mr. Downing thanked the HSRB members for their participation and adjourned the meeting at 3:14 p.m.

Respectfully submitted:

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

Certified to be true by:

Rebecca T. Parkin, Ph.D., M.P.H.
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

EPA HUMAN STUDIES REVIEW BOARD MEMBERS

Chair

Rebecca Parkin, Ph.D., M.P.H.
Professorial Lecturer, Environmental and Occupational Health and
Epidemiology and Biostatistics
Milken Institute School of Public Health
The George Washington University
Washington, DC

Vice Chair

Jewell H. Halanych, M.D., M.Sc.
Assistant Professor
Internal Medicine Residency Program
University of Alabama at Birmingham
Montgomery, AL

Members

Gary L. Chadwick, Pharm.D., M.P.H., C.I.P.
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HRP Consulting Group, Inc.
Training and Consulting in Human Research Protections
Fairport, NY

Liza Dawson, Ph.D.
Research Ethics Team Leader
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National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, MD

George C. J. Fernandez, Ph.D.
Statistical Training Specialist
SAS Institute, Statistical Training and Technical Services
Sparks, NV

Kyle L. Galbraith, Ph.D.
Human Subjects Protection
Carle Foundation Hospital
Urbana, IL

Members (continued)

Edward Gbur, Jr., Ph.D.
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Randy Maddalena, Ph.D.
Physical Research Scientist
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William J. Popendorf, Ph.D.
Professor Emeritus
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Logan, UT

Kenneth Ramos, M.D., Ph.D., Pharm.B.
Associate Vice President
Precision Health Sciences
Professor of Medicine
Arizona Health Sciences Center
Tucson, AZ

Suzanne M. Rivera, Ph.D., M.S.W
Vice President for Research and Technology Management
Case Western Reserve University
Cleveland Heights, OH

Jun Zhu, Ph.D.
Professor of Statistics and of Entomology
Department of Statistics
University of Wisconsin – Madison
Madison, WI

Attachment B

FEDERAL REGISTER NOTICE ANNOUNCING MEETING

[*Federal Register* Volume 79, Number 201 (Friday, October 17, 2014)]
[Notices]
[Pages 62437–62439]
From the *Federal Register* Online via the Government Printing Office [www.gpo.gov]
[FR Doc No: 2014–24757]

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ENVIRONMENTAL PROTECTION AGENCY

[EPA–HQ–ORD–2014–0750; FRL–9918–04–ORD]

Human Studies Review Board; Notification of a Public Meeting

AGENCY: U.S. Environmental Protection Agency.

ACTION: Notice.

SUMMARY: The EPA Office of the Science Advisor announces a public meeting of the Human Studies Review Board to advise the Agency on the ethical and scientific reviews of EPA research with human subjects.

DATES: This public meeting will be held on November 5, 2014, from approximately 10:00 a.m. to approximately 3:00 p.m. Eastern Time. Comments may be submitted on or before noon (Eastern Time) on Wednesday, October 29, 2014.

ADDRESSES: The meeting will be conducted entirely on the Internet using Adobe Connect and a conference call line. The conference call line is (866) 299–3188 and access code 2025647189. The Adobe Connect link is: http://epa.connectsolutions.com/hsrb. Enter the room as a guest providing your full name.
Comments: Submit your written comments, identified by Docket ID No. EPA–HQ–ORD–2014–0750, by one of the following methods:
Internet: http://www.regulations.gov: Follow the online instructions for submitting comments.
Email: ord.docket@epa.gov.
Mail: The EPA Docket Center EPA/DC, ORD Docket, Mail code: 28221T, 1200 Pennsylvania Avenue NW., Washington, DC 20460.
Hand Delivery: The EPA/DC Public Reading Room is located in the EPA Headquarters Library, Room Number 3334 in the EPA WJC West, at 1301 Constitution Avenue NW., Washington, DC 20460. The hours of operation are 8:30 a.m. to 4:30 p.m. Eastern Time, Monday through Friday, excluding federal holidays. Please call (202) 566–1744 or email the ORD Docket at ord.docket@epa.gov for instructions. Updates to Public Reading Room access are available on the Web site http://www.epa.gov/epahome/dockets.htm.
Instructions: The Agency's policy is that all comments received will be included in the public docket without change and may be made available online at http://www.regulations.gov, including any personal information provided, unless the comment includes information claimed to be Confidential Business Information or other information the disclosure of which is restricted by statute. Do not submit information that you consider to be CBI or otherwise protected through http://www.regulations.gov or

email. The http://www.regulations.gov Web site is an "anonymous access" system, which means the EPA will not know your identity or contact information unless you provide it in the body of your comment. If you send an email comment directly to the EPA without going through http://www.regulations.gov, your email address will be automatically captured and included as part of the comment that is placed in the public docket and made available on the Internet. If you submit an electronic comment, the EPA recommends that you include your name and other contact information in the body of your comment and with any electronic storage media you submit. If the EPA cannot read your comment due to technical difficulties and cannot contact you for clarification, the EPA may not be able to consider your comment. Electronic files should avoid the use of special characters, any form of encryption, and be free of any defects or viruses.

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

SUPPLEMENTARY INFORMATION:
Meeting access: Access to this Internet meeting is open to all at the information provided above.
Procedures for providing public input: Interested members of the public may submit relevant written or oral comments for the HSRB to consider during the advisory process. Additional information concerning submission of relevant written or oral comments is provided in Section I, "Public Meeting" under subsection D. "How May I Participate in this Meeting?" of this notice.

I. Public Meeting

A. Does this action apply to me?

This action is directed to the public in general. This Notice may, however, be of particular interest to persons who conduct or assess human studies, especially studies on substances regulated

[[Page 62438]]

by the EPA, or to persons who are, or may be required to conduct testing of chemical substances under the Federal Food, Drug, and Cosmetic Act or the Federal Insecticide, Fungicide, and Rodenticide Act. This notice might also be of special interest to participants of studies involving human subjects, or representatives of study participants or experts on community engagement. The Agency has not attempted to describe all the specific entities that may have interest in human subjects research. If you have any questions regarding this notice, consult Jim Downing listed under **FOR FURTHER INFORMATION CONTACT.**

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

In addition to using regulations.gov, you may access this **Federal Register** document electronically through the EPA Internet under the ''**Federal Register**'' listings at http://www.epa.gov/fedrgstr/.
Docket: All documents in the docket are listed in the http://www.regulations.gov index. Although listed in the index, some information is not publicly available, e.g., CBI or other information whose disclosure is restricted by statute. Certain other material, such as copyrighted material, will be publicly available only in hard copy. Publicly available docket materials are available either electronically in http://www.regulations.gov or in hard copy at the ORD Docket, EPA/DC, in the Public Reading Room. The EPA/DC Public Reading Room is located in the EPA Headquarters Library, Room Number 3334 in the EPA WJC West, at 1301 Constitution Avenue NW., Washington, DC 20460. The hours of operation are 8:30 a.m. to 4:30 p.m. Eastern Time, Monday through Friday, excluding federal holidays. Please call

(202) 566–1744 or email the ORD Docket at ord.docket@epa.gov for instructions. Updates to Public Reading Room access are available on the Web site (http://www.epa.gov/epahome/dockets.htm). The Agency's position paper(s), charge/questions to the HSRB, and the meeting agenda will be available by the middle of October 2014. In addition, the Agency may provide additional background documents as the materials become available. You may obtain electronic copies of these documents, and other related documents that are electronically, from the regulations.gov Web site and the EPA HSRB Web site at http://www.epa.gov/hsrb/. For questions on document availability, or if you do not have access to the Internet, consult Jim Downing listed under **FOR FURTHER INFORMATION.**

C. What should I consider as I prepare my comments for EPA?

You may find the following suggestions helpful for preparing your comments:
1. Explain your views as clearly as possible.
2. Describe any assumptions that you used.
3. Provide copies of any technical information and/or data that you used to support your views.
4. Provide specific examples to illustrate your concerns and suggest alternatives.
5. To ensure proper receipt by the EPA, be sure to identify the Docket ID number assigned to this action in the subject line on the first page of your response. You may also provide the name, date and **Federal Register** citation.

D. How may I participate in this meeting?

You may participate in this meeting by following the instructions in this section. To ensure proper receipt by the EPA, it is imperative that you identify Docket ID No. EPA–HQ–ORD–2014–0750 in the subject line on the first page of your request.

1. *Oral comments*. Requests to present oral comments will be accepted up to noon Eastern Time on Friday, October 31, 2014. To the extent that time permits, interested persons who have not pre-registered may be permitted by the Chair of the HSRB to present oral comments during the call. Each individual or group wishing to make brief oral comments to the HSRB is strongly advised to submit their request (preferably via email) to Jim Downing, under **FOR FURTHER INFORMATION CONTACT** no later than noon, Eastern Time, Friday, October 31, 2014, in order to be included on the meeting agenda and to provide sufficient time for the HSRB Chair and HSRB Designated Federal Official to review the meeting agenda to provide an appropriate public comment period. The request should identify the name of the individual making the presentation and the organization (if any) the individual will represent. Oral comments before the HSRB are generally limited to five minutes per individual or organization. Please note that this includes all individuals appearing either as part of, or on behalf of, an organization. While it is our intent to hear a full range of oral comments focused on the science and ethics issues under discussion, it is not our intent to permit organizations to expand the time limitations by having numerous individuals sign up separately to speak on their behalf. If additional time is available, further public comments may be possible.

2. *Written comments*. Submit your written comments prior to the meeting. For the Board to have the best opportunity to review and consider your comments as it deliberates on its report, you should submit your comments on or before noon (Eastern Time) on Wednesday, October 29, 2014. If you submit comments after this date, those comments will be provided to the Board members, but you should recognize that the HSRB members may not have adequate time to consider those comments prior to their discussion during the meeting. You should submit your comments using the instructions in Section I., under subsection C., ''What Should I Consider as I Prepare My Comments for the EPA?'' In addition, the agency also requests that persons submitting comments directly to the docket also provide a copy of their comments to Jim Downing listed under **FOR FURTHER INFORMATION CONTACT.** There is no limit on the length of written comments for consideration by the HSRB.

E. Background

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

1. *Topics for discussion.* At its meeting on November 5, 2014, EPA's Human Studies Review Board will consider scientific and ethical issues surrounding these topics:

   a. A new scenario design and associated protocol from the Agricultural Handler Exposure Task Force, LLC describing proposed research to monitor dermal and inhalation exposure of pesticide handlers who manually open containers of granular pesticide products and perform open pour loading of the granules into application equipment.

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   b. A published report by Frampton et al. (2002) of an intentional exposure human study measuring the effects of nitrogen dioxide exposure on airway and blood cells.

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

Dated: October 9, 2014.
Robert Kavlock,
Interim Agency Science Advisor.
[FR Doc. 2014–24757 Filed 10–16–14; 8:45 am]
BILLING CODE 6560–50–P

Attachment C

U.S. ENVIRONMENTAL PROTECTION AGENCY
HUMAN STUDIES REVIEW BOARD
NOVEMBER 2014 PUBLIC MEETING AGENDA

Wednesday, November 5, 2014

HSRB WEB SITE: http://www.epa.gov/osa/hsrb/
Docket Telephone: (202) 566 1752
Docket Number: EPA–HQ–ORD–2014–0750

10:00 a.m. **Convene Public Meeting—**Jim Downing, Designated Federal Officer, Human Studies Review Board (HSRB), Office of the Science Advisor, EPA
Conference Call Operations—Rebecca Parkin, Ph.D., M.P.H., HSRB Chair
Introduction of Board Members—Rebecca Parkin, Ph.D., M.P.H., HSRB Chair
Opening Remarks—Toby Schonfeld, Ph.D., Human Subjects Research Review Official, EPA

Session 1: **A new scenario design and associated protocol from the Agricultural Handler Exposure Task Force, LLC describing proposed research to monitor dermal and inhalation exposure of pesticide handlers who manually open containers of granular pesticide products and perform open pour loading of the granules into application equipment**

10:15 a.m. **EPA Science Review Highlights—**Jeff Evans (Office of Pesticide Programs [OPP], EPA)
10:25 a.m. **Board Questions of Clarification—**Rebecca Parkin, Ph.D., M.P.H. (HSRB Chair), EPA staff
10:40 a.m. **EPA Ethics Review Highlights—**Ms. Kelly Sherman (OPP, EPA)
10:50 a.m. **Board Questions of Clarification—**Rebecca Parkin, Ph.D., M.P.H. (HSRB Chair), EPA staff
11:05 a.m. **Public Comments**

11:10 a.m. Board Discussion

If the proposed research is revised as suggested in EPA's review and if the research is performed as described:

Charge to the Board—Science:

- Is the research likely to generate scientifically reliable data, useful for assessing the exposure of workers who perform open-pour loading of granular pesticides?

Charge to the Board—Ethics:

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

12:00 p.m. Lunch

12:55 p.m. Reconvene—Roll Call

Session 2: A published report by *Frampton et al.* (2002) of an intentional exposure human study measuring the effects of nitrogen dioxide exposure on airway and blood cells

1:00 p.m. **EPA Science Review Highlights—**LT Jonathan Leshin, Ph.D. (OPP, EPA)
1:10 p.m. **Board Questions of Clarification—**Rebecca Parkin, Ph.D., M.P.H. (HSRB Chair), EPA staff
1:25 p.m. **EPA Ethics Review Highlights—**Ms. Kelly Sherman (OPP, EPA)
1:35 p.m. **Board Questions of Clarification—**Rebecca Parkin, Ph.D., M.P.H. (HSRB Chair), and EPA staff
1:50 p.m. **Public Comments**
1:55 p.m. **Board Discussion**

Charge to the Board—Science:

- Is the Frampton el al. (2002) study scientifically sound, providing reliable data?
- If so, is this study adequate for quantitative use in support of an inhalation risk assessment for the use of nitrogen dioxide as a medical equipment sterilant?

Charge to the Board—Ethics:

- Does the study meet the applicable requirements of 40 CFR Part 26, Subpart Q?

2:50 p.m. Adjourn