November 28, 2017

EPA-HSRB-XX-X

Dr. Jennifer Orme-Zavaleta
EPA Science Advisor
Office of the Science Advisor
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Subject: October EPA Human Studies Review Board Meeting Report

Dear Dr. Orme-Zavaleta,

The United States Environmental Protection Agency (EPA or Agency) requested that the Human Studies Review Board (HSRB) provide scientific and ethics review of one item titled **Protocol for a Study for Measurement of Potential Dermal and Inhalation Exposure during the Application of Paint Containing an Antimicrobial using an Airless Sprayer.** The Board's responses to the charge questions and detailed rationale and recommendations are provided in the enclosed final meeting report.

Signed,

Liza Dawson, PhD
Chair
EPA Human Studies Review Board

INTRODUCTION

On October 25, 2017, the United States Environmental Protection Agency's (EPA or Agency) Human Studies Review Board (HSRB or Board) met to address the scientific and ethical charge questions related to a **Protocol for a Study for Measurement of Potential Dermal and Inhalation Exposure during the Application of Paint Containing an Antimicrobial using an Airless Sprayer**

REVIEW PROCESS

The Board conducted a public meeting on October 25, 2017. Advance notice of the meeting was published in the *Federal Register* as "Human Studies Review Board; Notification of a Public Meeting" (EPA, October 11, 2017, Pages 47204 and 47205).

Following welcoming remarks from Agency officials, the Board began its review of the study, **Protocol for a Study for Measurement of Potential Dermal and Inhalation Exposure during the Application of Paint Containing an Antimicrobial using an Airless Sprayer.**

The Board heard two presentations from EPA for this study protocol, consisting of the Agency's review of scientific and ethical aspects of the proposed study. This Final Report of the meeting describes the HSRB's discussion, recommendations, rationale and consensus in response to each charge question for the study.

At the meeting, Agency staff first presented their review of the science and the Board asked the Agency presenters clarifying questions. The staff then described their review of the ethical aspects and the Board asked clarifying questions about those. The HSRB solicited public comments and next asked Agency staff to read the Charge Questions under consideration. The Board discussed the science question first and then the ethics question. The Chair called for a vote to confirm concurrence on a summary statement in response to each charge question.

For their evaluation and discussion, the Board considered materials presented by EPA staff at the meeting, related materials and documents provided by the study sponsors, the Agency's science and ethics reviews of the studies, and oral responses from Agency staff and from study investigators in attendance at the meeting.

Scientific Review: Charge to Board:

Is the protocol "A Study for Measurement of Potential Dermal and Inhalation Exposure During the Application of Paint Containing an Antimicrobial using an Airless Sprayer" likely to generate scientifically reliable data, useful for assessing the exposure of those who apply products containing antimicrobial pesticides as preservatives using an airless sprayer?

Board Response

The Board concludes that the protocol as presented is likely to generate scientific reliable data, useful for assessing the exposure of those who apply products containing antimicrobial pesticides as preservatives using an airless sprayer, provided the changes requested by EPA and the changes requested by the HSRB below are implemented. The Board also has specific recommendations and clarifications to be made in the study protocol, as described below.

HSRB Detailed Recommendations and Rationale:

HSRB reviewed information provided in advance of the meeting, as well as the EPA scientific and ethics presentations provided at the meeting. The Board noted and agreed with the changes in the protocol document, both major and minor, that were recommended by EPA reviewers. In addition, the Board identified further details that need to be clarified or modified in the protocol. The HSRB requests that these changes be made and submitted for EPA review prior to submission to the reviewing IRB. The Board's detailed recommendations are discussed below.

1) Clarification of rationale for paint volumes in the study protocol

The study sponsor is asked to revise the justification of the volumes of paint used within the protocol. The protocol currently states that subjects will use 10, 15, and 30 gallons as target

paint volumes during the different scenarios, indicating that the 30 gallon limit is driven by typical use patterns. This reasoning is not supported by the survey of professional painters that was performed and provided by the study sponsors, in which some respondents used volumes as high as 50 gallons. It was clarified that the upper volume of 30 gallons is needed based on feasibility, given that this volume may take 6 hours to spray and the sponsors wanted to minimize the total time of subjects in each scenario given the additional tasks required during the study day. The Board recognizes the rationale for a 3-point reference of exposure based on the 10, 15, and 30 gallon usage that will allow extrapolation to 50 gallons. At the same time, the Board notes that the study may not be capturing exposure for high risk groups (i.e., large companies) that either use higher amount of paint volumes and work longer hours, or have multiple painters working at the same time that could increase exposures. This potential high risk group is indicated on the survey. The Board recommends that this potential higher exposure be acknowledged in the protocol, as well as noting that the survey is based on a small sample size.

Documentation of site and work factors: The success of the study in capturing representative exposure monitoring data relies on the study identifying and varying the most relevant factors influencing dermal and air exposures during airless spraying. In attempt to generate representative exposure monitoring data, the protocol includes variations in paint volume, propiconazole concentration and subjects between monitoring events, and room size and features (horizontal and vertical surfaces) within monitoring events. In addition, subjects are allowed to vary the spray gun nozzles and wands, the ventilation (through use of fans and windows), and the use of wipe cloths ("painters rags"). HSRB suggests the careful documentation of the site factors [ventilation sources (windows, fans), fixtures, surface areas and orientation (vertical vs. horizontal), as well as behavioral factors (use of rags, wiping of dermal areas, choice of nozzle and wands] that influence air and dermal exposures to aid in data interpretation. When appropriate, both the frequency and duration of the factors influencing exposure should be captured. The Board recommends creating a field collection report form that includes all the work-practice and environmental factors (i.e., field variables) that will be collected and the time over which these factors will be collected (e.g., every 15 minutes, as they change).

2. Provide exposure information and rationale for respirator use choice.

The Board recommends that the use of respirators during the study be more thoroughly addressed in the protocol. In order to identify whether respirator use should be mandatory and if so, the appropriate respirator type, the study sponsor should clearly identify the potential hazards (contaminants) based on the type of paint and sprayers used, and determine the level/concentration of the contaminant(s) in the air. First, the study sponsor should provide an updated Safety Data Sheet (SDS) for the Sherman Williams Superpaint. The SDS provided includes discrepancies, indicating a respirable dust/total dust hazard, yet suggesting the use of a combination organic vapor/particulate respirator. If the only hazard is dust/total dust, then a particulate respirator is adequate. Should a volatile organic compound (VOC) be present and an organic vapor respirator be required, details on the VOC should be listed within the Composition/Information on the Ingredients Section of the SDS. In addition, the study sponsor should provide data on the concentration of the hazard during the task, either by performing sampling or by providing an industry accepted concentration. Once the concentration is determined, the study sponsor can use the United States Occupational Safety and Health Administration (OSHA) Permissible Exposure Limit (PEL) for each of the identified hazards to guide respirator selection. Respirators should be required if concentration of the contaminant is above OSHA PEL and can be voluntary if the concentration during activity is below OSHA PEL. Based on the protection factor and hazard characteristics (particle versus VOC) the correct type of respirator should be chosen. Based on whether respirators are required or voluntary, different requirements are specified under OSHA.[1] Training may be achieved by providing appendix d[1] or showing a video.[2] If respirator use is required, then, fit testing and medical clearance is also needed. Fit testing is suggested rather than required, if the study sponsor is going to provide N95 respirators for voluntary use. OSHA provides a protocol for qualitative fit testing which requires a kit and equipment, and can be performed by following the protocol (i.e., by study personnel). The respirator fit testing can likely be performed within 30 minutes.[3] The study sponsors should

[1] See: https://www.osha.gov/video/respiratory_protection/voluntaryuse_transcript.html Workers wearing respirators, regardless of voluntary versus required need training. Specifically the content of Appendix D from the OSHA standard (https://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=9784).

[2] https://www.osha.gov/video/respiratory_protection/voluntaryuse.html

[3] see protocol - https://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=standards&p_id=9780 .

provide a range of N95 respirators to account for different face types. The study sponsor should allow, but not require workers to bring their own respirators. Allowing for the use of a study supplied respirator or for subjects to bring their own respirator, would allow for a wider and potentially more representative sample of painters in the area. Furthermore, should respirator use be deemed to be voluntary, subject selection can proceed without requiring that subjects be willing to wear a respirator.

3. Clarify the margin of exposure (MOE) calculations used in the study The Board requests that the study sponsor review and clarify the dermal absorption value for propiconazole that was used in the MOE calculations by EPA. The initial value used in the 2006 re-registration document appears to be 40%, but 100% was referred to in a correspondence by EPA to Janssen Pharma. Subsequent study data provided by Janssen and accepted by EPA placed that value at 1% for paints. Based on the discussion at the meeting, the Board's view is that this is an accurate representation of how the value of 1% was selected in the MOEs that are in effect for this proposed study.

The Board's second concern regarding MOEs was the apparent lack of harmonization in the MOEs that EPA has presented and those that appear in an EU document from 2015.[4] The Board requests that the Agency comment on the possible source(s) of lack of harmonization between the EPA and the EU assessments of MOEs for propiconazole.

5. Limitations with respect to using professional painters versus consumer users

AEATF II suggests enrolling subjects who are professional painters as they best represent the typical user of airless paint spraying equipment. Professional painters may represent the worst case exposure scenario as they have higher exposures due to the higher volume of paint that they use as compared to consumer painters. However, dermal exposure may be higher among

[4] Regulation (EU) No 528/2012 concerning the making available on the market and use of biocidal products Evaluation of active substances. Assessment Report: Propiconazole; Product-type 7; (Film preservatives); January 2015; Finland.

consumers (non-professional painters) due to inexperience with operating the equipment and the resulting direct contact and splashing with the paint. Therefore, the results under a study conducted according to this protocol may underestimate dermal exposure to antimicrobials among inexperienced consumer users using an airless sprayer. Additional detail on the risk assessment assumptions when extrapolating to consumers who use airless paint spraying equipment may be warranted. These limitations should be discussed in the protocol.

6. Statistical issues

Given the practical and ethical constraints associated with the protocol, the design that utilizes three volumes of paint sprayed, the same two propiconazole concentrations for each volume, and three randomly assigned subjects (monitoring events) to each of the six combinations is reasonable.

As noted above, the proposed protocol randomization plan restricts subject selection to professional painters, which means that the data cannot be used to draw conclusions about homeowners and other non-professional painters without assumptions supported by objective evidence that it is reasonable to do so. The homeowner and other non-professional painter population may have much different personal characteristics than the professional painter population, which may impact the transfer of the study conclusions.

Since the AEATF II task force will not provide any statistical analysis of the data, the following comments are directed to EPA's proposed analysis as described in Section C.5 (page12) of the EPA Memorandum titled "Science and Ethics Review of AEATF II Airless Sprayer Paper Scenario Design and Protocol for Exposure Monitoring" dated September 27, 2017. The Board agrees with EPA's overall regression modeling approach that considers the logarithm of the exposure as a function of the logarithm of the amount of active ingredient. The Board did find it somewhat unusual that the presentation appeared to initially state somewhat unequivocally that the final model would be a single straight line for all spray-propiconazole combinations with an assumed slope of one.

EPA does go on to indicate that several very reasonable alternative models would be investigated both statistically and graphically if the assumed single straight line was not adequate. From a statistical modeling perspective, it is common practice to begin by fitting more complex models and eliminating non-significant terms to reach a final model that then would be checked for consistency with the data.

For analysis of any of the initial regression models, it would be important to consider the inclusion of other potentially important predictors; e.g., temperature, relative humidity, actual painting time, actual amount of paint used, actual surface area painted, and ceiling height, against which studentized residuals could be graphed to check for patterns. Characteristics of potentially useful non-quantitative variables such as nozzle type should be recorded and used for color (or symbol) coding of the observations in studentized residual plots to identify potential biases that they may cause.

The Board had one final comment on Attachment 2, Section 2.1 (i) on pages 40 and 41 of the EPA Memorandum. The idea that under several simplifications and other assumptions the statistical power for dermal or inhalation exposure could be 100% does not seem at all reasonable. A power of 100% would appear to guarantee a sample size that would provide a zero probability of an incorrect conclusion from the study.

7. Additional recommendations

The Board recommends clarifying the following issues in the study protocol.

Formulation type: EPA's scientific review of the protocol included a slide of the formulation types (e.g., powder, liquid, handheld) that are targeted for study. Please include the information on that slide as a reference in the protocol for understanding the matrix and the definition of formulation as used in this study. This also adds context to the need for the study in the special category of "airless paint spraying".

Choice of paint: Please include the rationale for choosing this particular product for study. In discussion, it was mentioned that this paint was used in the previous study with consumers and

commonly used with airless paint sprayers and this clarification could be included in the protocol.

Documentation of personnel training: The protocol does not mention training of personnel. A training protocol would be appropriate to prepare and train study staff on data collection procedures. The training protocol could be referenced or included as an appendix.

Protocol for dermal samplers: Please include a wait time to allow drying of the paint on the dosimeters for removal, and also add further details on how the dosimeters will be handled with care. In addition, please provide the rationale for not including the researchers' gloves in the testing after they handle the dosimeters. In Volume 4 of 4 in the SOPs (page 83) there is a procedure for taking off the dosimeters which mentions that the gloves from the researcher should be discarded, but the rationale for this is not provided.

Handwashing: Page 42-43 of protocol, please clarify if the subjects wash their hands on site, before starting to paint. This is mentioned on the consent form on page 4 but not in the protocol.

Use of ladder: Please clarify if a ladder over 6 feet will be used, and when or if fall protection will be used, as fall protection is required by OSHA at 6 feet and above. Slipping on tarps is also a possibility.

Videotaping: Videotaping is first mentioned on page 48 and then 60 (AEATF II Project ID: AEA10). The protocol should elaborate on this videotaping (i.e., is the videotaping done throughout the exposure period; is taping stationary or following the subject; focused on the spraying activities, or on all activities).

Alternate location: Page 37 of protocol should clarify if alternates are brought to the site on the day of testing, or if an alternate is only contacted if they are needed, and is brought to the site on another day.

Snacks: Page 45 mentions that the subjects may choose to eat or use tobacco. Please clarify if the subjects bring their own food.

Ethics Review: Charge to the Board

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

Board Response

HSRB Recommendation

The HSRB concludes that the research presented in the protocol "A Study for Measurement of Potential Dermal and Inhalation Exposure During the Application of Paint Containing an Antimicrobial Using an Airless Sprayer" (AEA10) is likely to meet the applicable requirements of 40 CFR part 26, subparts K and L, if modified in the ways detailed below.

HSRB Detailed Recommendations and Rationale

The Agency's rules at 40 CFR part 26, subpart K detail the practical and ethical requirements for IRB review and approval of third-party research that the Agency intends to consider in connections with its actions. The rules at 40 CFR part 26, subpart L prohibit the Agency from relying on third-party research for such consideration if that research involves intentional exposure to a pesticide of human subjects who are children or pregnant or nursing women. These regulatory requirements are sufficiently satisfied in the ways described below.

1. **IRB Information**

This study has been reviewed and approved by Schulman IRB, a commercial IRB that has been accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP) since June 2008. They are registered with the Office for Human Research Protections (IRB Registration #00000971) and indicate on their website that they have

undergone six consecutive audits by the U.S. Food and Drug Administration (FDA) with no findings, the most recent of which took place in November 2016.

The Schulman IRB panel roster provided by AEATF II in Volume 3 of their supplied documentation demonstrates that the panel that reviewed and approved this study in August 2017 satisfies the IRB membership requirements set forth in subpart K, paragraph 1107. A Schulman IRB panel will also review any changes made to the study in light of HSRB and EPA recommendations prior to their implementation.

2. Minimization of Risks

Risks associated with research procedures will be minimized in the following ways:
As noted on page 18 of the protocol and detailed in its supplementary materials, the surrogate test substance used in this study—propiconazole—has been selected due in part to its low toxicity level in mammals. It is an antimicrobial pesticide and fungicide commonly used in agriculture and is commercially available with a maximum concentration of 12,000 ppm. Its concentration in this study, either 1,200 ppm or 12,000 ppm, is consistent with what is already commercially available. As a result, the amount of test substance to which subjects are exposed should not be drastically dissimilar to what one may be exposed in the course of daily work activities. Further, individuals with known allergies or sensitivities to propiconazole or any triazole fungicide, as well as individuals with skin issues (such as psoriasis, eczema, or visible cuts) will be excluded from study participation.

Subjects will also have multiple physical barriers to protect them from the test substance. Subjects will be wearing two layers of clothing (long sleeved shirt and long pants over the dosimeters) to further minimize unnecessary dermal exposure. The protocol states that they will be provided with safety glasses with side-shields or goggles and must use their own half-face respirator when painting. The issue of respirators was a major point of discussion by the HSRB as noted above and the final plan regarding respirator use should be based on level and type of contaminants and OSHA standards for respirator use associated with those exposures.

To minimize the risk of allergic reactions to the latex materials and isopropyl alcohol used in the study, persons with known allergies or sensitivities to these materials will be excluded from study participation.

To minimize the risk of heat stress, the study will take place in winter in Florida, where the researchers report that average high temperatures are rarely above 80 degrees Fahrenheit. The duration of actual paint spraying during a subject's participation will be approximately two to six hours, which seems consistent (if not slightly below) with what a typical day of painting would be for a professional painter. The study will also follow AEATF II SOP 11B.1 (Heat Stress), which provides ample guidance for researchers to monitor environmental conditions that may contribute to heat-related stress, including hourly checks of the heat index if the ambient temperature reaches at least 70 degrees Fahrenheit. If necessary, researchers will open doors and windows to lower ambient temperature and will make floor fans or blowers available to subjects. Water and sports drinks will also be made available to subjects, who are encouraged to take breaks whenever they feel the need. Researcher personnel are trained to recognize symptoms of heat stress and will be present to monitor subjects. The SOP also indicates that the research team will "make arrangements to provide access to local emergency medical assistance if it becomes necessary" (SOP 11B.1, Section 4.6.a) and the protocol states that "a physician, nurse, emergency medical technician (EMT), or physician's assistant unaffiliated with the researchers will be hired for the study and will be on site for each monitoring event and will provide medical support if needed" (p. 33). Lastly, an informational poster titled "Controlling Heat Stress Made Simple" will be posted in both English and Spanish at the test site.

Risks associated with moving multiple five-gallon buckets of paint are also minimal, but further minimized by enrolling only professional painters who already perform such activities and are healthy enough to do so.

There are minor psychological risks associated with the study participation, given that female subjects must take a urine pregnancy test in order to participate and subjects will need to disrobe in front of researchers when donning and doffing their dosimeters. These activities and the potential risks are clearly delineated in the informed consent document. The process for minimizing psychological risks associated with a pregnancy test is described below. To

minimize psychological discomfort associated with dressing and undressing, subjects will do so only in front of a researcher of the same gender and in a private area.

There may also be minor confidentiality risks in the event that study data is unexpectedly released or accessed. However, this risk is very minor given that none of the data collected about subjects are of an especially sensitive nature. SOP 11J.1 (Obtaining Informed Consent) describes appropriate methods to keep study data secure and accessible only to qualified research personnel, and those methods adhere to Good Laboratory Practice guidelines at 40 CFR part 160. Any photos included in the study's final report will omit subject faces and identifying tattoos. In the event that the study data is published, those data will be de-identified before publication. As noted below, the results of pregnancy tests will not be recorded. As a result, there are no significant confidentiality concerns related to this study.

Lastly, subject compensation does not appear coercive or extravagant, given the study procedures and the time subjects will spend participating in the study. Interested persons who attend an informed consent meeting but elect not to participate will receive $20, while subjects who enroll in the study and participate or serve as an alternate will receive $200. Since subjects will either spend a full working day participating in the study *or* block off a full working day for their participation, this amount seems appropriate.

3. Subject Selection

Subjects who enroll in the study must be professional painters with a minimum of three months experience using an airless sprayer to apply architectural paint within the last five years (protocol, p. 17). As described in the scientific review, the inclusion of only professional painters is because professionals are more likely to use airless sprayers than non-professional (consumer) painters and because professionals generally use higher volumes of paint than non-professionals. Further, professionals are more likely to have the appropriate knowledge and experience to be able to operate an airless sprayer and repeatedly handle large buckets of paint, thereby minimizing the risks associated with those study activities.

The study's inclusion and exclusion criteria are clearly defined in both the study protocol and informed consent document and are appropriate for minimizing risks associated with study participation, as noted above. Any employees or the spouse of any employee of companies represented by AEATF, Sherwin-Williams, the American Chemistry Council, or Lange Research and Consulting will be excluded in order to minimize the risks of bias or coerced participation. There is an upper age limit of 65 for subjects, which the protocol notes is because the "study requires some physical activities." The Board recommends that this upper age limit be removed to allow healthy subjects older than 65 to participate, if they choose to do so, unless there is a clear rationale and justification for the age limit

4. Informed Consent

Informed consent discussions will be conducted in a one-on-one setting unless potential subjects want their family member(s) to attend. Potential subjects will be given two copies of the informed consent document—one to keep and one to sign—and those persons will have the opportunity to take a copy of the consent document home with them to discuss the study with family or friends prior to agreeing to participate. The informed consent document is clearly written, contains all required elements of informed consent detailed in subpart K, and gives potential subjects a helpful overview of what study participation will entail.

A bilingual member of the research team who is able to communicate in both English and Spanish will be available for consent discussions when potential subjects indicate a preference for speaking in Spanish. That team member will also be present during monitoring events that involve subjects who prefer to speak Spanish. Certified Spanish-language translations of the informed consent document and recruitment materials have also been included with the materials the Board has reviewed (certification provided by WeLocalize Life Sciences).

Lastly, AEATF II SOP 11J.1 (Obtaining Informed Consent) provides an overview of the measures researchers will take to ensure that subjects comprehend what study participation entails, including the study's risks and benefits (or lack thereof). There is also a "Subject Study Comprehension" verification worksheet attached to that SOP, which includes a series of open-

ended questions that researchers will pose to subjects that they must successfully answer before being able to participate in this study (Volume 4, p. 159).

Exclusion of Children and Pregnant or Nursing Women

This study intends to enroll subjects between the ages of 18 and 65, so no minors will participate in the research. As noted in the protocol (p. 16), subject ages will be verified by a government issued photo ID when potential subjects meet with a member of the research staff for the informed consent discussion.

AEATF II Standard Operating Procedure (SOP) 11A.1 (Human Subject Management Pregnancy Testing and Nursing Status) clearly details steps taken to ensure that pregnant or lactating women do not participate in the study. First, researchers will review the study's exclusion criteria—including the exclusion of pregnant or nursing women—with potential subjects during the initial consent discussion. At that time, interested women will also be informed that they must take an over-the-counter urine pregnancy test when arriving to the test site on the day of their participation. These pregnancy tests will be provided to female subjects by the study team at no cost to subjects. Female subjects will self-administer the test in a private bathroom. After taking the test and viewing her results, a female subject will be asked if she wants to continue study participation. If she declines, her participation in the study is discontinued though she will still receive compensation for her time and inconvenience. She will not be asked why she wishes to discontinue participation and her test result will not be recorded. If she wishes to continue, the results of the pregnancy test will be verified by a female researcher to ensure that the test result is negative. In this case, researchers will record that a pregnancy test was performed in compliance with SOP 11A.1. In both cases, the pregnancy tests will then be discarded in an opaque bag. These measures appear appropriate and do not introduce unnecessary risks or burdens on the women who wish to participate in this study.

HSRB Recommendations

The HSRB recommends the study team implement the following changes in order to further ensure protection of the rights and welfare of research subjects:

1. As noted above, remove the upper age limit on study participation so that adults of any age who otherwise satisfy the study's inclusion and exclusion criteria are able to participate in the study, unless a clear justification is provided for the age limit.

2. Please revise recruitment materials to indicate that a government-issued photo ID is required for study participation.

3. The Occupational Safety and Health Administration (OSHA) recommends a minimum of two hearing protection device options be provided to allow workers with a variety of ear types and preferences to be protected. Please revise the study protocol accordingly to provide at least two types of hearing protection options.

4. Revise the informed consent document to include risks associated with using a small ladder.

5. Revise the informed consent document to describe the videotaping that will take place during the study, and give subjects the option of indicating if they do not wish to be videotaped.

6. In the study's subject screening materials, subjects are currently asked if they are allergic to the test product, propiconazole. To promote subject understanding, please revise this question to ask whether subjects have ever had an allergic response to paint products.

7. Please address the concern regarding respiratory protection as detailed elsewhere in this Report.