EPA-HSRB-22-1

Dr. H. Christopher Frey, Ph.D.

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Washington, DC 20460

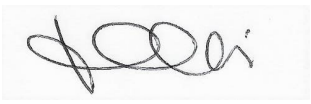
Subject: April 27, 2022, EPA Human Studies Review Board Meeting Report

Dear Dr. Frey,

The United States Environmental Protection Agency (EPA) requested that the Human Studies Review Board (HSRB) provide a scientific and ethics review of a completed study involving human participants. On April 27, 2022, the HSRB considered the Electrostatic Sprayer Scenario 2b from study AEA14 submitted by the Antimicrobial Exposure Assessment Task Force II (AEATF II). Briefly, the goal of the completed study was to determine dermal and inhalation exposures of workers using electrostatic sprayers (ESS) indoors to sanitize and disinfect surfaces. Data from the study was used to determine unit exposures for the use of an ESS for surface sanitizing and disinfecting of indoor areas within commercial and institutional spaces such as hotels and hospitals.

The HSRB's responses to the charge questions presented at the meeting on April 27, 2022, along with the rationale for their conclusions and additional considerations and recommendations are provided in the enclosed final meeting report.

Signed,



Jennifer Cavallari, ScD, CIH

Chair, EPA Human Studies Review Board

INTRODUCTION

On April 27, 2022, the United States Environmental Protection Agency (EPA or Agency) Human Studies Review Board (HSRB or Board) met to address the scientific and ethical charge questions related to a completed study from the Antimicrobial Exposure Assessment Task Force II (AEATF II) AEA14 Scenario 2b: Electrostatic Spray (ESS) Human Exposure Monitoring Study. In accordance with 40 CFR 26.1603 and 26.1604, the EPA sought HSRB review of the protocol for this research on June 20, 2020, and July 21-22, 2020, and for the completed study at this meeting.

REVIEW PROCESS

The Board conducted a public meeting on April 27, 2022. Advance notice of the meeting was published in the *Federal Register* as "Human Studies Review Board; Notification of a Public Meeting" (EPA, FRL-9328-01-ORD). This Final Report of the meeting describes the HSRB's discussion, rationale, recommendations, and consensus in response to the charge questions on ethical and scientific aspects of the completed research.

The Agency staff presented their review of the scientific and ethical aspects of the completed research, with each presentation followed by clarifying questions from the Board. The HSRB solicited public comments and next proceeded to address the charge questions under consideration. The Board discussed the science and ethics charge questions and developed a consensus response to each question. For each of the charge questions, the Chair called for the Board to vote to confirm concurrence on a summary statement reflecting the Board's response.

For their evaluation and discussion, the Board considered materials presented at the meeting, study reports, related materials and documents provided by the study sponsors, the Agency's science and ethics reviews of the study, as well as oral comments from Agency staff and the investigators during the HSRB meeting discussions. A partial list of documents provided to the HSRB is available at https://www.epa.gov/osa/april-27-2022-meeting-human-studies-review-board. In addition to the documents listed on the website, the HSRB was provided the AEA14 Scenario 2b Study Report.

A Study for Measurement of Potential Dermal and Inhalation Exposure During Pressurized Hand-Wand Spraying of Antimicrobial Products (AEA14); Scenario 2b: Measurement of Potential Dermal and Inhalation Exposure During Indoor Electrostatic Spraying of Sanitizers and Disinfectants.

Charge to the Board - Science:

Did the research summarized in "A Study for Measurement of Potential Dermal and Inhalation Exposure During Pressurized Hand-Wand Spraying of Antimicrobial Products (AEA14); Scenario 2b: Measurement of Potential Dermal and Inhalation Exposure During Indoor Electrostatic Spraying of Sanitizers and Disinfectants" generate scientifically reliable data, useful for assessing the exposure of those who apply antimicrobial pesticides using electrostatic sprayers?

HSRB Response:

The HSRB concludes that the research summarized in the study AEA14: "A Study for Measurement of Potential Dermal and Inhalation Exposure During Pressurized Hand-Wand Spraying of Antimicrobial Products; Scenario 2b: Measurement of Potential Dermal and Inhalation Exposure During Indoor Electrostatic Spraying of Sanitizers and Disinfectants" provides scientifically reliable data, useful for assessing the exposure of individuals who apply antimicrobial pesticides using electrostatic sprayers.

The HSRB also has specific comments, recommendations, and additional minor points that are described below.

Science review

This study was conducted to assess dermal and inhalation exposure of workers sanitizing/disinfecting indoor surfaces using electrostatic sprayer (ESS) cleaning methods and to develop unit exposures for people who use ESS to sanitize and/or disinfect indoor surfaces with an antimicrobial product.

The protocol for this completed study was previously reviewed by the EPA and the HSRB under the larger hand-wand sprayer study protocol for ethical and scientific design on June 22, 2020, and July 21-22, 2020. This ESS study is only one of the scenarios from the larger hand-wand study (i.e., Study AEA14, Scenario 2b: ESS). In its review of the protocol, the HSRB concluded that the research proposed would result in a scientifically and ethically valid study, provided the EPA's and the HSRB's recommendations were addressed prior to the initiation of the research. Some of the recommended protocol changes by EPA and the HSRB were as follows: ensure sprayers are turned on, ensure a record of experience in using these sprayers, collection of aerosol and vapors, evaluation the linear relationship between exposure and amount applied, and ability to capture variation. A variety of statistical recommendation and comments were also made. The recommendations from both EPA and HSRB were adequately addressed.

The AEATF II's study objective is to monitor inhalation and dermal exposures to be used as inputs in exposure algorithms to predict future exposures to persons sanitizing/disinfecting indoor surfaces by ESS cleaning methods. The mixing/loading exposure data were developed in prior AEATF II studies, because there are multiple antimicrobial formulations (e.g., soluble concentrates, ready-to-use solutions, etc.). Therefore, that data needed to be generated in separate studies. In this study, participants from the janitorial/cleaner industry sanitized/disinfected hotel conference center/hotel rooms with one of the three types of ESS: backpack, handheld, and cart.

Three different brands were used: Clorox Total 360 cart system, Victory brand sprayer (backpack and handheld), and EMist (backpack and cart). Subjects sprayed a variety of locations within the facility, including hotel guest rooms and meeting rooms of various sizes and configurations. Each used one of three types of ESS (Victory, ByoPlanet/Clorox, EMist) as a handheld sprayer, backpack sprayer, or cart sprayer. Subjects applied a target amount (0.5, 1, or 2 gallons) of a solution containing an EPA-registered sanitizer (Maquat® 5.5-M, DSV, 5.5% total quaternary ammoniums) diluted to target concentrations of 215 ppm to 860 ppm. The surrogate chemical was the one of the four quats, quat Didecyldimethylammonium chloride (DDAC), had respective concentrations from 36.3 to 145 ppm. The assignment to a target amount for the subjects was randomized. Subjects were informed of safety and other protocols (e.g., no eating during the study). Drinking was allowed and seen as part of normal behavior. If subjects went to the bathroom, their hands were first washed to recover target compounds. Some observations of behavior were made. For example, most subjects sprayed by starting from the far end of the room and worked their way backward. One Monitoring Event (ME) seemed not to follow directions, some seemed to walk into the spray they released, and a couple touched the surfaces they sprayed. These may all be part of behaviors that may exist in the field and potentially increase exposures.

Subjects wore inner whole-body dosimeters (WBD) underneath an outer whole-body dosimeter comprising of a long-sleeved shirts, and long pants. In addition, the subjects wore a painter's cap, and an inner hat dosimeter (two pieces of gauze stapled to the inside of the painter's cap), and no gloves. Subjects wore two personal air-sampling pumps, one attached to OVS air-sampling tube and one attached to a parallel particle impactor (PPI) cassette containing a PVC filter. Both types of sampling media were attached to the subjects' shirt collars in their

breathing zones for air concentration measurements during their spray activities. Field fortification recoveries (conducted three times) were used to adjust the residue concentrations measured for the subjects. Lab spike recoveries were also used to adjust the residue concentrations measured for the subjects.

Unit Exposures (UEs) are generated from this study. UEs are expressed as "handler" exposure normalized by the amount of active ingredient (a.i.) handled by participants in scenario-specific exposure studies (e.g., mg a.i. exposure/lb a.i. handled). EPA uses these UEs generically to estimate exposure for other chemicals having the same and/or different application rates.

The AEATF II's objective for this study design is to be 95% confident that key statistics of normalized exposure are accurate within 3-fold. Specifically, the upper and lower 95% confidence limits should be no more than 3-fold (K=3) higher or lower than the estimates for each of the geometric mean, arithmetic mean, and 95th percentile unit exposures. To meet this objective, AEATF II proposed an experimental design with 18 MEs for "professional/commercial" employed subjects cleaning/sanitizing hard surfaces.

The documents provide great detail on electrostatic sprayers and the test compounds. All equations used in the calculations are included in the documents (ESS Scenario Report, part 1, page 53). ESS Scenario Report (part 1, page 56) includes information on the experience of the subjects using the various sprayers. Rooms were sprayed and areas were recorded (only to consider the dimensions of the rooms). The ESS Scenario Report and EPA scientific review contain many pictures of a subject applying the compound and layouts and diagrams of the rooms where the study occurred. IRB modifications and all meeting minutes are included in the report.

The six protocol deviations and five SOP deviations are presented in detail in the AEATF II ESS Scenario Report as well as the EPA scientific review. The HSRB agrees with the EPA assessment that none of the protocol or SOP deviations adversely affected the study outcome. In addition, the study was stamped as conforming to GLP standards, with two deviations thought not to affect study results. Inspections and audits were conducted by an external firm "Perspective Consulting Inc." over the course of the study.

Briefly, the square feet of rooms sprayed for the MEs in the 0.5-gallon group ranged from 2,071 to 7,316 ft^2. In the 1-gallon group, the square feet of the rooms sprayed ranged from 6,180 to 19,698 ft^2. In the 2-gallon group, the square feet of the rooms sprayed ranged from 4,142 to 40,434 ft^2. (AEATF 2021, page 95). Of the 22 subjects enrolled, there were 5 females and 17 males. Subjects' ages ranged from 24 to 70 years old. Subjects had from 1 month to 3 years' experience using an ESS, with frequency of ESS use ranging from daily to once a month.

Ambient sampling also took place in the room pre activities indicting no presence of DDAC and post sampling indicated that predominant air concentrations declined after 30 minutes. The minimum and maximum temperatures during the 18 MEs ranged from 62.4 to 76.9 degrees Fahrenheit, and relative humidity from 53.9 to 78.9%.

The highest residues were found on the hands (80% of dermal exposures), which is expected as no gloves were used during the scenario. The second highest residues were found on the head. The dermal UE for the long pants/long-sleeves, no hat, no gloves scenario averaged 621 mg/lb ai (Table 1, page 3 of EPA Scientific Report). The highest exposures (1,063 mg/lb ai) and (1,012 mg/lb ai) were seen for subjects using the EMist and Victory Sprayers. EMist design appears to allow dripping back unto the hand. There was only one ME (ME 1) for which OVS

tubes did not contain measurable DDAC residues. Dermal exposures were adjusted for the area of the eyes. Inner dosimeters levels were low

Inhalation unit exposure averaged 6.01 mg/lb ai as a total inhalable dose (Table 1, page 3 of EPA Scientific Report). The highest inhalation unit exposure was 15,968 µg/lb. Researchers noted that individual spray practices influenced exposure, but that the spray equipment also influenced exposure potential. Use of the 12-inch wand extension that can be used on Victory ESS seemed to reduce both dermal and inhalation exposures (creating more distance between the subject and the target compound), but there was not enough data to conclude a statistically significant reduction of exposure with the use of the wand extension.

Statistical Review

The geometric mean empirical model (GMS), geometric standard deviation empirical model (GSDS), arithmetic mean log normal random sample model (AMU), and arithmetic mean empirical model (AMS,) 95th percentile log normal random sample model (P95U), and the 95th percentile empirical model (P95S) dermal unit exposures are accurate within 3-fold with 95% confidence.

A k-factor is most appropriate for determining how well a statistic describes its population parameter. If a specific estimate has a k-factor of three or less, the sample statistic will be accurate to within 3-fold of the population estimate 95% of the time. Most of the K factors are less than 3. The sample size is sufficient.

The average and standard deviation for GM and AM inhalation unit exposures for total inhalable aerosols are accurate within 3-fold with 95% confidence for the empirical and lognormal random sample models. The P95 inhalation unit exposures are within 3-fold with 95% confidence for the lognormal random sample model but not the empirical model.

The inhalation unit exposures for respirable aerosols satisfy the 3-fold objective for GMS and GSDS. They are close to this 3-fold objective for AMS, AMU, and P95U, whereas the P95S has a fold relative accuracy > 3.

The statistical analysis shows evidence aligning with log-log-linearity with a slope of 1. An ideal result of the log-log-linearity test is an estimated positive slope with a confidence interval including one and excluding zero, indicating that the assumption of log-log-linearity with slope 1 is supported.

In the study, the confidence intervals for the slope include one and exclude zero for dermal, inhalation 8-hr TWA, and inhalation dose. Therefore, the assumption of independence was rejected, and the assumption of log-log-linearity with slope 1 was supported. Thus, the "unit exposure" approach for the dermal, inhalation 8-hr TWA and inhalation dose is reasonable. Therefore, the study's proposed statistical methods are appropriate to answer the research question. Therefore, the research generated scientifically reliable data, valid for assessing the exposure of those who apply antimicrobial pesticides using electrostatic sprayers.

Recommendations:

The HSRB has the following set of recommendations and minor points to consider:

- There is extensive discussion on the different sprayers and the variability these introduce. The sprayers were all purchased new. It would be useful to include a discussion on whether any differences are expected with new versus older/heavily used sprayers, how maintenance and upkeep (or lack of) may affect exposures, and also if there would be any impact of different sized tanks.

- Protocol deviation #3 has embedded 4 distinct deviations and should be listed separately and reflected on separately.
- EPA should consider if any effort should be made to observe activities related to ingestion exposure (e.g., wiping/licking of the lips/mouth during spraying) in these studies. This may be a missed opportunity to use the data for modeling in the future.
- Future studies should include other states to increase the variability in workers and what may be regional cleaning methods and strengthen the study.
- The exposure estimates support a dramatic reduction in dermal exposure when wearing long-pants/sleeves. EPA should consider whether the long-sleeve scenario appropriately reflects the dermal exposure of workers when cleaning and sanitizing while using an ESS. It is likely that workers wear short-sleeves, especially hospital-based custodians who may have access to short-sleeved scrubs.

Charge to the Board - Ethics:

Does the available information support a determination that the research was conducted in substantial compliance with the applicable requirements of 40 CFR part 26, subparts K-L?

Response: The available information supports the study "A Study for Measurement of Potential Dermal and Inhalation Exposure During Pressurized Hand-Wand Spraying of Antimicrobial Products (AEA14); Scenario 2b: Measurement of Potential Dermal and Inhalation Exposure During Indoor Electrostatic Spraying of Sanitizers and Disinfectants" was conducted in substantial compliance with the requirements of 40 CFR part 26, subparts K-L.

Ethics review:

40 CFR 26 subpart K mandates studies minimize risk to subjects, equitably select subjects, seek and appropriately document informed consent, make adequate provisions to ensure the safety of subjects, and protect the privacy of subjects and confidentiality of data.

Subject Selection and Recruitment

The selection of subjects was equitable, and the recruitment procedures were conducted ethically and without apparent coercion. Participants must have been at least 18 years of age to participate. Participants were recruited via flyers and online and print advertisements. Subjects were screened over the phone to ensure compliance with inclusion criteria; those who met the criteria and were interested were scheduled for a virtual consent meeting.

The study did not enroll pregnant women and being "pregnant, lactating or nursing, or unwilling to self-administer an OTC pregnancy test before participating" was an exclusion criterion. Additionally, female subjects were required to self-administer an OTC pregnancy test, which was confirmed by a female member of the research team. There was no intentional exposure of any human subject who is a pregnant woman, a nursing woman, or her child. (40 CFR part 26 Subpart Q §26.1703)

Informed Consent Process

Participants were provided both written and oral information regarding their eligibility, the purpose of the study, study procedures including risks associated with their participation, Covid-19 related precautions, and their ability to end their participation at any time for any reason (or no reason at all). Consent meetings were held via Zoom to minimize risk of Covid-19 exposure to interested participants. While recruitment was conducted only in English, two participants consented via bilingual research team member per their preference. The Spanish-

language consent forms were approved by the IRB. Comprehension of the material in the consent was ensured, all participants electronically signed the consent form, and their participation was incentivized, including the consent meetings, filling out study questionnaires, a fit-test appointment, and their monitoring day. (FIFRA §12(a)(2)(P))

Risks and Benefits

Subject risk was effectively minimized via the inclusion and exclusion criteria, current occupational knowledge and experience using the ESS, standard procedures conducted during monitoring events (including monitoring for Covid-19), properly fitted respirators, and eyewear. Subjects were allowed to take breaks to hydrate, were warned about exertion and heat-related stress, and all procedures were conducted in air-conditioned facilities. A medical professional was present on site during all monitoring days. No adverse events were reported, but the company was prepared to pay for any study-related injury or illness. Several amendments and deviations from the approved protocol were reported during the course of the study, however, there is no indication that these deviations or protocol modifications changed the risk-benefit ratio, introduced novel or additional risks to subject welfare and health, or impacted the validity of the scientific outcomes.

Independent Ethics Review

The protocol was approved by the Advarra IRB, and subsequent EPA, and HSRB reviews were conducted of this protocol in 2020. All found that, if conducted as proposed, then the study would meet the applicable requirements of 40 CFR 26 subparts K and L.

Summary

Based on the study protocol and supplied documents, it appears that the study was conducted according to appropriate ethical standards: an independent ethics review was conducted, the subject selection was equitable, risks to subjects were adequately minimized, informed consent was obtained and documented, and no procedures impaired or impacted informed consent. Regarding the applicable ethical regulations, no pregnant, nursing or lactating women were enrolled in this study and there was no intentional exposure of any human subjects who is a pregnant or nursing woman. Participants had to be over 18 years of age to participate so there was no intentional exposure to any human subjects who are children. Finally, subjects were adequately consented, their comprehension of the consent materials was obtained, possible risks associated with participation were covered, and the voluntariness of their participation was reinforced.