EPA-HSRB-19-1

Office of the Science Advisor
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Subject: October 23rd, 2018 EPA Human Studies Review Board Meeting Report

Dear Dr. Orme-Zavaleta,

The United States Environmental Protection Agency requested that the Human Studies Review Board (HSRB) provide scientific and ethics review of a protocol submitted by the Antimicrobial Exposure Assessment Task Force (AEATF II) entitled *A Study for Measurement of Potential Dermal and Inhalation Exposure During Antimicrobial Applications Involving Immersion, Dip, and Soak*. The Board's responses to the charge questions and detailed rationale and recommendations for their conclusions on this study are provided in the enclosed final meeting report.

Signed,

Liza Dawson, PhD
Chair
EPA Human Studies Review Board

Advance notice of the meeting was published in the *Federal Register* as "Human Studies Review Board; Notification of a Public Meeting" (EPA, FRL-9984-60-ORD) This Final Report of the meeting describes the HSRB's discussion, recommendations, rationale and consensus in response to the charge questions on ethical and scientific aspects of the Antimicrobial Exposure Assessment Task Force (AEATF II) protocol, *A Study for Measurement of Potential Dermal and Inhalation Exposure During Antimicrobial Applications Involving Immersion, Dip, and Soak.*

Agency staff presented their review of scientific and ethical aspects of the study, with each presentation followed by clarifying questions from the Board. The HSRB solicited public comments and then took up the charge questions under consideration. The Board discussed the science and ethics charge questions and developed a consensus response to each question in turn. 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 presentations given by EPA staff at the meeting, oral comments from Agency staff and from the investigators during the meeting discussions, and the Agency's written reviews which were provided to the Board prior to the meeting.

**Charge to the Board- Science:**

Is the protocol "A Study for Measurement of Potential Dermal and Inhalation Exposure During Antimicrobial Applications Involving Immersion, Dip, and Soak" likely to generate scientifically reliable data, and is useful for assessing the exposure of those who use products containing antimicrobial pesticides for sanitizing surfaces and equipment?

**Response to the charge question:**

The protocol "A Study for Measurement of Potential Dermal and Inhalation Exposure During Antimicrobial Applications Involving Immersion, Dip, and Soak" is likely to generate scientifically reliable data, and is useful for assessing the exposure of those who use products containing antimicrobial pesticides for sanitizing surfaces and equipment provided the changes requested by EPA and the changes requested by the HSRB below are taken into account and

implemented. The Board also has specific recommendations and clarifications to be made in the study protocol, and additional minor points which are described in the discussion 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 requested by the EPA. In addition, the Board identified further details that need to be added to the protocol. Specifically, the Board suggests that the temperature of the water being used in each scenario be measured and captured. The rationale is that attention to air temperature is given for the volatility and movement of the chemical in air, and this might also be affected by water temperature. Water temperature also has the potential to damage or open pores of the skin.

**Additional recommendations**

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

**Height of air sampler**. The height of the air sampler on the participant and the height of the participant should be recorded. This may have implications on the overall air exposure as participant height will dictate distance from the exposure source.

**Surface area cleaned during bucket and sponge/rag scenario**. In determining the location where the study is to be performed, we recommend that the site has a large enough amount of surface with (i.e. enough chairs, counters, tables, etc) to allow a participant to perform the task for a full 1 hour.

**Protocols to account for loss during drinking and other activities**: The primary measures of exposure are dermal and inhalation, but the subject might also be instructed to avoid drinking, eating, or smoking during the activity. And if they do, the protocol should be specific as to how to account for loss due to this activity (e.g., similar to the description of rest room use by the participant). Similarly, as the face and head are not being measured, any wiping of the face with hands or arms could result in loss.

**Statistical review.** In general, the proposed statistical design and analysis of the protocol are appropriate for EPA's intended use of the data. In particular, the following comments were made.

- Reasonable justification was provided for restricting subject selection to commercial workers based on the risk being driven by larger amounts of the active ingredient handled compared to typical consumers. Although the results could still be extrapolated to the general population, this would represent a study weakness in doing so.
- For each of the three scenarios, multiple configurations would be used to get a range of diverse situations. However, as noted by the Science reviewers, more specifics on the actual ranges should be stated at the study design phase.
- According to EPA, there is not enough power to discover proportionality of concentration and exposure for the 3-compartment sink and COP scenarios. The EPA recommendation for those two scenarios is to increase the range of the concentrations of the test substance in the treatment solution in order to increase the statistical power. Justification of proposed sample sizes as amended by EPA should meet the accuracy goals. In addition, it was stated that if these goals were not met based on the data collected in the study, follow up actions would be taken, including possible additional sampling.

EPA would follow previously established statistical procedures for data analysis of these types of studies. The statistical analysis of data collected on 54 monitoring events (MEs),18 MEs per scenario, is adequate. A simple linear regression model for the logarithm of the exposure with an intercept term and with a slope coefficient multiplied by the logarithm of the concentration is utilized. Confidence intervals for the slope can be utilized in order to examine whether the slope is different from 1 or from 0. Q-Q plots of the normalized exposures can be utilized to measure the lognormality assumption. The studentized residuals can be utilized to measure the model performance of the final model. These statistical procedures were deemed appropriate.

In addition, should simple linear regression not provide an adequate fit to the data, EPA would consider other regression models and probability distributions as alternatives to the standard procedures. Data values less than the limit of quantitation (LOQ) would be assigned a value of

one-half of the LOQ for calculating total exposure. This choice is one of several commonly used substitutions.

In general, the Board deemed the statistical procedures to be appropriate, with modifications as requested by EPA's review.

**Charge to the Board—Ethics:**

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

**Response to the charge question:**

EPA staff have made a number of ethics and privacy comments and recommendations. The Board has reviewed these and agrees with recommendations EPA staff have made. With the changes recommended by EPA staff the Board believes this study complies with the applicable ethical standards [40 CFR 26, subparts K and L, as well as FIFRA 12(a)(2)(P)].

**HSRB detailed recommendations and rationale:**

The proposed study will assess worker exposure to an antimicrobial applied via three methods: (1) bucket & sponge/rag, (2) 3-compartment sink, and (3) Clean-Out-of-Place (COP). The protocol is well written and generally clear. The objectives of this study cannot be achieved via studies in vitro or in vivo in animals, so the study must be conducted with humans. Minors (under 18) and women who are pregnant or lactating are appropriately excluded, in accordance with EPA human subjects standards for intentional exposure studies. With the addition of recommendations by EPA staff, including differences for each experimental condition, inclusion and exclusion criteria are appropriate. EPA staff have also made recommendations with regard to the range of ADBAC concentrations to be tested (Table 1 of EPA review) and the sample size to increase the statistical power of the study. Insofar as these recommendations strengthen the science of this trial, they also contribute to the ethics, since sound science that benefits society is the foundation of an ethical study. There are no direct benefits to the individuals participating in this study, though the knowledge gained may benefit them and others using these agents. Risks appear no more than those that the subjects would be exposed to on a daily basis in their workplaces. The benefit/risk balance is favorable as the knowledge gained will benefit society generally and those applying antimicrobials in multiple settings.

Subjects will be recruited and participation is voluntary with informed consent of the subjects. Subjects will receive a payment $20 for attending the consent meeting, and a payment of $100 to $200 depending on subject experience and which antimicrobial application method they will be involved with. As noted by EPA staff, these amounts are appropriate as compensation for the subjects' transportations expenses, time and varying levels of skills/experience required for the different methods. They are not so large as to provide an undue inducement to participate.

Both English and Spanish versions of the informed consent forms will be available. Staff will be available to translate, or potential subjects may bring a family member or friend.

This protocol has been reviewed and approved by Advarra's IRB and will be reviewed again once changes recommended by EPA staff and the EPA HSRB are made. The Board does not see any ethical barrier to the conduct of the study and believes it will meet the applicable requirements of 40 CFR part 26, subparts K and L.