June 25, 2014

EPA-HSRB-14-01

Robert Kavlock, Ph.D.
Interim EPA Science Advisor
Office of the Science Advisor
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Subject: April 8-9, 2014 EPA Human Studies Review Board Meeting Report

Dear Dr. Kavlock,

The United States Environmental Protection Agency (EPA or Agency) requested that the Human Studies Review Board (HSRB) provide scientific and ethics reviews of two new scenario designs and associated protocols and two newly proposed protocols. The Board's responses to the related charge questions and their additional comments are enclosed in a final meeting report for the April 8-9, 2014, meeting. This letter indicates the key findings from the Board's reviews.

A New Scenario Design and Associated Protocol from the Antimicrobial Exposure Assessment Task Force (AEATF-II) Describing Proposed Research to Monitor Dermal and Inhalation Exposure During Manual Pouring of Solid Formulation Antimicrobial Products (AEA07)

Science

- The Board concluded that this research, if modified in accordance with the suggestions made by the Agency and the Board, is likely to generate scientifically reliable data. The residential component of the research will be useful for assessing the exposure of those who pour solid formulation antimicrobial products into swimming pools using a wide range of techniques. The occupational component of this research will be useful for assessing exposures over a narrower but practical range of parameters.

Ethics

- The Board concluded that the protocol submitted for review, if modified in accordance with EPA (Leighton, Sherman & Cohen, 2013) and HSRB recommendations, is likely to meet the applicable requirements of 40 CFR 26, subparts K and L.

A New Scenario Design and Associated Protocol from the AEATF-II Describing Proposed Research to Monitor Dermal and Inhalation Exposure During Application of Latex Paint Containing an Antimicrobial Pesticide Product Using Brush and Roller Equipment (AEA09)

Science

- The Board agreed with the Agency's conclusion that, if modified according to Agency and HSRB recommendations, the proposed research to monitor dermal and inhalation exposure during application of latex paint containing an antimicrobial pesticide using brush and roller equipment is likely to produce scientifically reliable data. The Board also agreed that the modifications to the protocol suggested by the EPA (Leighton, Sherman & Cohen, 2014a) be accomplished before initiation of the study.

Ethics

- The documents submitted to the EPA and the HSRB do not fully meet the regulatory requirements. However, the Board concluded that the protocol submitted for review will likely meet the applicable requirements of 40 CFR part 26, subparts K and L, if: 1) it is modified in accordance with EPA (Leighton, Sherman, & Cohen, 2014a) and HSRB recommendations; 2) necessary approvals are obtained; and 3) additional documents are provided to the Agency for review.

A New Protocol from the AEATF-II Describing Proposed Research to Measure the Removal Efficiency of 1,2-Benzisothiazol-3(2H)-one (Known as BIT) from Hand Surfaces Using an Isopropyl Alcohol/Water Wipes and Wash Procedure (AEA08)

Science

- With the exception of one member, the Board concluded that the proposed research is likely to generate scientifically reliable data, useful for determining the removal efficiency of BIT from the hands due to dermal exposure associated with the use of latex paint and non-paint liquid solutions containing BIT, provided that the protocol is modified to address the issues raised by EPA and the HSRB.

Ethics

- The documents submitted to the EPA and the HSRB do not fully meet the regulatory requirements. Despite this, the Board concluded that this protocol will likely meet the applicable requirements of 40 CFR 26, subparts K and L if: 1) it is modified in accordance with EPA (Leighton, Sherman & Cohen, 2014b) and HSRB recommendations; 2) necessary approvals are obtained; and 3) additional documents are provided to the Agency for review.

A New Protocol from the U.S. Department of Agriculture Describing Proposed Research to Determine the Bite Protection Level of Repellent Treated Clothing for the United States Military

Science

- The Board concurred that the proposed protocol will likely generate scientifically reliable data for estimation of bite protection efficacy of impregnated clothing, if improvements in the overall study design enumerated by EPA (Sweeney & Sherman, 2014) and the Board are adequately considered.

Ethics

- The Board concluded that the protocol submitted for review, if modified in accordance with EPA (Sweeney & Sherman, 2014) and HSRB recommendations, is likely to meet the applicable requirements of 40 CFR 26, subparts K and L.

Sincerely,

Rebecca T. Parkin, PhD, MPH
Chair
EPA Human Studies Review Board

NOTICE

This report has been written as part of the activities of the EPA Human Studies Review Board, a Federal advisory committee providing advice, information and recommendations on issues related to scientific and ethical aspects of human subjects research. This report has not been reviewed for approval by the Agency and, hence, the contents of this report do not necessarily represent the view and policies of the Environmental Protection Agency, nor of other agencies in the Executive Branch of the Federal government, nor does the mention of trade names or commercial products constitute a recommendation for use. You may obtain further information about the EPA Human Studies Review Board from its website at http://www.epa.gov/osa/hsrb. You may also contact the HSRB Designated Federal Officer, via e-mail at ord-osa-hsrb@epa.gov

In preparing this document, the Board carefully considered all information provided and presented by the Agency presenters, as well as information presented by public commenters. This document addresses the information provided and presented within the structure of the charge by the Agency.

US ENVIRONMENTAL PROTECTION AGENCY
HUMAN STUDIES REVIEW BOARD

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*Not a participant at this meeting.

INTRODUCTION

On April 8 and 9, 2014, the United States Environmental Protection Agency's (EPA or Agency) Human Studies Review Board (HSRB) met to address the scientific and ethical charge questions related to two new scenario designs and associated protocols and two newly proposed protocols.

- A New Scenario Design and Associated Protocol from the Antimicrobial Exposure Assessment Task Force (AEATF-II) Describing Proposed Research to Monitor Dermal and Inhalation Exposure During Manual Pouring of Solid Formulation Antimicrobial Products (AEA07)
- A New Scenario Design and Associated Protocol from the AEATF-II Describing Proposed Research to Monitor Dermal and Inhalation Exposure During Application of Latex Paint Containing an Antimicrobial Pesticide Product Using Brush and Roller Equipment (AEA09)
- A New Protocol from the AEATF-II Describing Proposed Research to Measure the Removal Efficiency of 1,2-Benzisothiazol-3(2H)-one (Known as BIT) from Hand Surfaces Using an Isopropyl Alcohol/Water Wipes and Wash Procedure (AEA08)
- A New Protocol from the U.S. Department of Agriculture Describing Proposed Research to Determine the Bite Protection Level of Repellent Treated Clothing for the United States Military

REVIEW PROCESS

The Board conducted public face-to-face meetings in Arlington, Virginia, on April 8 and 9, 2014. Advance notice of the meeting was published in the *Federal Register* as "Human Studies Review Board; Notice of Public Meeting" (USEPA, 2014).

Following welcoming remarks from Agency officials, the Board heard presentations from EPA on each of the four protocols listed above. This Final Report of the meeting describes the discussion, recommendations and rationale in response to each charge question for each protocol. The Agency also made a presentation about the Repellency Awareness Graphic. The lead author of the HSRB Work Group on the Return of Individual Research Results described the group's workshop deliberations and report. Brief sections summarizing these latter two agenda items and the Board's discussions about them are included at the end of this meeting report.

For each protocol, Agency staff first presented their review of the science components of the proposal and the Board asked the Agency presenters clarifying questions about the science. The staff then described their review of the ethical aspects of the proposal and the Board asked clarifying questions about the ethical issues. The Board solicited public comments and next asked Agency staff to read the Charge Questions for the proposed protocol under consideration. The Board discussed the science question first and then the ethics question. Upon conclusion of the discussion of each question, the Chair called for a vote on a summary statement in response to that question.

For their evaluation and discussion, the Board considered materials presented at the meeting, oral comments, one letter from the public, and Agency background documents (*e.g.*, the proposed study protocols; AEATF governing documents; standard operating procedures and policies; institutional review board documentation; statistical methods and estimates); and the Agency's science and ethics reviews of the proposed protocols. A comprehensive list of background documents is available online at http://www.epa.gov/hsrb/.

CHARGE TO THE BOARD AND BOARD RESPONSE

A New Scenario Design and Associated Protocol from the Antimicrobial Exposure Assessment Task Force (AEATF-II) Describing Proposed Research to Monitor Dermal and Inhalation Exposure During Manual Pouring of Solid Formulation Antimicrobial Products

Overview of the Scenario Design and Associated Protocol

AEATF-II's solid pour study (**AEA07**) is designed to measure dermal and inhalation exposures of workers and consumers when they manually pour solid antimicrobial products. The surrogate chemical for this study will be cyanuric acid (CYA). In this protocol, "pour" means either pour or scoop; scoops will be used in scenarios with larger containers. Two separate solid formulations are to be used; a powder and a granular product. Each formulation will be handled by the two sets of participants: workers and consumers. The research will be conducted in a warehouse in Concord, Ohio.

Four scenarios will be studied: occupational pouring of granules, occupational pouring of powders, residential [*i.e.;* consumer] pouring of granules, and residential pouring of powders. Each scenario will have 18 monitoring events (MEs) and three amounts of active ingredient handled (AaiH). The duration of pouring and the sizes and types of source and receiving containers will vary within each scenario. The same 18 worker participants will be studied in the two occupational scenarios, and the same 18 residential participants will be assessed in the two consumer scenarios. The occupational group will wear chemical resistant gloves while pouring a formulation into a mixing tank. The consumer group will not wear gloves as they pour the product into a swimming pool. Each ME will include measurement of dermal exposure by using inner and outer dosimeters, as well as hand and face washes. Breathing zone air concentrations for each ME will be measured using personal air monitors.

Participants for the study will be recruited from occupational and residential populations. The workers will be sought from experienced professional applicators (users), while the consumers will be recruited from residential groups with experience treating their swimming pools with solid formulations. The AEATF-II study is designed to represent real-world use of commercially available solid antimicrobial products. The study is intended to identify high-end levels of potential exposure. The Agency plans to use the resulting data in algorithms to estimate occupational and residential handlers' daily exposures from pouring or scooping solid antimicrobial products and to assess the related risks they would experience.

EPA's review of the proposed protocol was completed on September 10, 2013, and presented to the HSRB on April 8, 2014. The protocol was reviewed and approved by an independent human

subjects review committee, Shulman Associates IRB (SAIRB) of Sunrise, FL. The Agency made recommendations for improvements in both scientific and ethics aspects of the protocol.

Science

Charge to the Board

- Is this research likely to generate scientifically reliable data, useful for assessing the exposure of those who pour solid formulation antimicrobial pesticide products?

Board Response to the Charge

HSRB Recommendation

The Board concluded that this research, if modified in accordance with the suggestions made by the Agency and the Board, is likely to generate scientifically reliable data. The residential component of the research will be useful for assessing the exposure of those who pour solid formulation antimicrobial products into swimming pools using a wide range of techniques. The occupational component of this research will be useful for assessing exposures over a narrower but practical range of parameters.

HSRB Detailed Recommendations and Rationale

The Board agrees with the Agency's statement that revisions in the protocol need to be made regarding assigning specific AaiH, scoop sizes, and containers; requiring all subjects to wear particulate dust masks; and providing additional details about the airflow orientation. Furthermore, the AEATF-II will need to provide hand wash removal efficiency information to allow EPA to correct for incomplete residue removal from the hand sampling.

The Board expressed concerns with (1) the narrow range of use conditions proposed for all occupational users, in contrast to the wider range of product particle diameters, heights of "free-fall" while pouring, local air velocities, geometries of the receiving container, the subsequent time spent in the immediate vicinity of the pour, and the difference between new versus used gloves; (2) the potential for the occurrence of one or more identifiable random events (especially within the residential scenario)[1] that have the potential to overwhelm the underlying effect of proportionality over a 10-fold range in the residential AaiH; (3) the weak scientific justification offered to differentiate the studies being proposed to assess exposures while pouring solid antimicrobial products from studies already approved to assess exposures while pouring solid agricultural pesticides; (4) the inclusion of more research design features to enhance the likelihood of successful statistical tests of the results; and (5) the age and quality of toxicity studies used in support of the safety of a chemical or agent. Each of these five concerns is explained further below.

1. Most of these concerns are predicated upon factors generally known to affect a user's exposure and dose while pouring a solid (nonvolatile) product (*e.g.*, Popendorf, 2006, pp. 216-229). A summary of those factors is provided below.

[1] Such as a wet hand contacting the dry formulation while scooping or during a major spill.

- *The product's distribution of particle diameters.* Aerodynamic diameter influences the amount of airborne particles that are generated by a given action (*e.g.*, pouring from a given height), the settling velocity of these airborne particles, and (in combination with local air velocity as discussed below) the distance they travel before (or while) contributing to dermal (and airborne exposures), respectively. In typical indoor air (discussed below), particles larger than about 100 μm will fall a distance of one meter within about 1-4 meters of their source, meaning they will usually fall out of the air and land on a nearby surface (the floor if not before). Particles smaller than about 50 μm have a good chance of staying airborne for more than 10 meters. Sedimentation has almost no effect on particles 10 μm or less in diameter, and these small particles will behave similar to vapors.

- *The distance the product is allowed to "free fall"* from its pouring container to its receiving container. The amount of aerosol generated during a pouring operation is in some way proportional to the magnitude of the gravitational energy released when the poured material encounters either the bottom of the receiving container or the material already accumulating within that container. The protocol for occupational uses proposes a consistent free fall distance of about 18 inches by pouring the chemical through the top of a loading tank 36 inches tall and approximately half-full of circulating water. This distance is reasonable but may or may not represent a high-end exposure scenario for manual pouring. The range of free falls for the residential handlers is somewhat wider and will be replicated by allowing each person to stand, bend, or kneel on a deck surrounding a swimming pool and while pouring down to the water level.

- *The local horizontal air velocity, i.e.*, both its direction and speed. Horizontal air currents in typical mechanically ventilated rooms are generally in the range of 20 to 40 feet per minute (fpm) but can exceed 100 fpm.[2] Room air currents in a given location may also be vertical[3] and will usually have momentary vertical components due to turbulence. Particles will fall any time their settling velocity exceeds the local upward air speed; this process is called sedimentation. Thus, either some knowledge is needed of local air currents between the pour site and the person pouring or/and some steps need to be taken within the protocol to assure those conditions are varied among MEs.

- *The geometry of the receiving container*, in particular the height of its opening in relation to the user and any constraints like a lid. Receiving container geometry (in combination with the above factors) will affect the portions of a user's body on which most of the airborne particles will be deposited due to sedimentation and the magnitude of those depositions. While the height of receiving containers in industrial settings can easily range from floor level (or below) to above waist height, the protocol specifies a fixed height of approximately 36". Again, that height is reasonable but may or may not represent a high-end exposure scenario. However, the effect of a lid is more uncertain and thus problematic within the protocol. A partial lid will reduce the plume, but increase the likelihood of spillage and create a nearby large horizontal surface on which large diameter particles will collect via

[2] What some would call a "draft".

[3] Especially near a warm or hot source or where a horizontal air current encounters a vertical barrier.

sedimentation. The latter can increase real-world exposures whether or not the person who pours also cleans (*e.g.*, wipes or vacuums) those nearby surfaces.[4]

- *The subsequent time spent in the immediate vicinity of the pour* attending to some ancillary aspect of the pouring and mixing process. Time spent nearby (in combination with the above) will affect airborne exposures as well as the amount of airborne particles that will be deposited on the person due to sedimentation. The most common example is mixing while and immediately after pouring, but these are not included in this protocol. Industrial uses of biocides[5] usually require some form of mixing to assure suspension of the product. This mixing is most efficient if conducted during and immediately after the pouring step, and the same person who pours usually also monitors that mixing process. Another task is some, at least rudimentary, cleanup. More cleanup is likely to occur where the receiving container has a lid. Thus, the same person is usually in the near vicinity of the pour and is exposed to any particles still suspended in the air that can contribute to both their airborne and dermal exposures for several minutes.

- *The use of personal protective equipment (PPE);* in this case, gloves and respirators. The protocol justifies the consistent use of gloves by occupational handlers, no gloves by consumers, and, if modified, consistent use of respirators by all. However, new gloves provided to each participant are not the same as gloves previously used multiple times by the same person to handle the same solid formulated product. Past studies of handlers using their own gloves have shown significant hand exposures, on the order of 50% of their whole-body dose, presumably because of the accumulation of small amounts of material over time (Popendorf, et al., 1995).

The narrow range of use conditions proposed for the occupational scenario will make it difficult to extrapolate to other use conditions or to assure that the test conditions represent high-end exposures. Some use can be made of scientific principles that pertain to the factors that are listed above; however, most of these effects are more qualitative than quantitative. Among the known factors, it was encouraging to hear that information regarding the particle size distribution of the surrogate product will be provided. There are limits to the range of free-fall and receiving container geometries that can be replicated in a purposive diversity study. The Agency has already asked the sponsor to provide additional details about the airflow. At the time of the meeting, the protocol appeared to require the researchers to report a heating ventilation and air conditioning (HVAC) air exchange rate. Unless a case can be made for how the air exchange rate will be used, there does not seem to be a need within this protocol to have "a facilities maintenance engineer with HVAC training or an industrial hygienist will document the HVAC system (if there is one) in the warehouse and measure the air exchange rate" (Leighton, Sherman & Cohen, 2013, p. 13).

However, a few suggestions were made to either increase diversity or better replicate real-world occupational settings. At 20 to 40 fpm, the air velocity in indoor settings is typically too weak to sense but can be measured and is predominantly from one direction at any given location. The HSRB recommended that the Agency consider requiring steps within the protocol to add some

[4] In fact, such accumulations left unattended could become the largest component of long-term time-weighted average (TWA) dermal exposures which are beyond the purview of this protocol.
[5] As well as, most other solid formulations being poured, even in agricultural settings.

variability to the effect of ventilation in the indoor setting and thereby compensate the expected consistent air velocity at any one test location.[6]

The Board also suggested that the EPA consider adding a step into the occupational protocol that would cause the ME to spend some time in the immediate vicinity of the receiving container subsequent to the pour, *e.g.*, five minutes. While any time so spent would add realism, adding some rudimentary cleanup to the lip of the receiving container, its lid, and any inadvertent spillage would add even more realism. Applying this step to all or a random portion of MEs is another design option.[7]

The HSRB noted that because all occupational users will wear gloves these data cannot be used to estimate exposures to such users without gloves.[8] The issue of differences between new versus used gloves is less clear; it is not feasible to provide used gloves to the occupational handlers.[9] A simpler although less satisfying step would be to multiply the whole-body dermal exposures measured with new gloves by 2× (based on pre-rule published data, Popendorf *et al.*, 1995), which is also indicative of the probable magnitude of this issue.

2. The residential protocol is much more complex than the occupational protocol. It involves having some residential handlers pour their solid product straight from its container, others using a scoop, and a portion of both pouring first into a bucket, pre-dissolve it, then pouring the liquid mixture into the pool. Other than the protocol covering such a wide diversity of conditions that will limit its applicability to other more narrowly defined handling tasks, the proposed protocol seems likely to do a very good job of assessing exposures to consumers treating a swimming pool.

The fact that residential users will not wear gloves is understandable, but it heightens the probability for otherwise minor variations in application practices to create major variations in measured exposures. One notable example would be someone scooping biocide with a wet hand. It is well known that powders or granulars will stick to wet skin better than dry skin. It is more likely for someone to have wet hands around a pool than in an industrial setting. A wet hand holding a scoop inserted into a container is more likely to contact the product than if just pouring from its package. While no predicted value can be put on the relative increase in measured exposure that such an event would cause, it seems likely to exceed the 10× range between the low median AaiH (3.3 lb. in Group 1) and high median AaiH (38 lb. in Group 3). In contrast,

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[6] For example, if all tests are to be conducted in the same location within the warehouse, each ME could be instructed to work on a designed but different side of the receiving container. If such instructions are deemed too intrusive, then at least the equipment available to each ME can be pre-positioned on a different side of the receiving container. In either case, at least four different sides should be used.

[7] A potentially important suggestion was later made that when adding variability into purposive diversity studies of this nature, it is preferable to add it via a randomization structure by creating a list of the sequence of combinations of variables to be tested rather than allowing the probability of small numbers to operate haphazardly

[8] Apparently no labels for use without gloves are anticipated; so this point is moot.

[9] Future research might be conducted to assess naturally accumulated residues inside gloves used in real occupational settings. Other future research might be conducted into creating artificially contaminated gloves and into how much of the residues inside such gloves (whether created naturally or artificially) would transfer to wearers.

occupational users might have major spills, but their gloves should limit the excursions within their measured exposures. Given the stated goals of this study, no preventive steps against such occurrences is suggested, but one can anticipate that such an eventuality is likely to have a major effect on the subsequent tests for proportionality of unit exposure values with AaiH. The Board recommended that the observer of these MEs be instructed to watch very carefully for and note such occurrences, especially since a wet hand scooping inside a container may occur out of the observer's sight.

3. The Board also expressed some concern that the justification for conducting these studies appears more descriptive than scientific, and at best qualitative rather than quantitative. The question was asked, assuming that proprietary issues can be overcome, could this data-need be satisfied by using the new AHETF exposure data generated by pouring agricultural pesticides? Of particular interest are the conditions pertaining to prior pre-rule data from AHE39 and the previously reviewed protocols in AHE80 (Evans, Parsons & Sherman, 2010). AEATF-II cited five key differences between pouring solid antimicrobial products and pouring solid agricultural pesticides (Leighton, Sherman & Cohen, 2013, p. 21). However, most of these differences are either not serious, could be overcome, or/and are not rooted in science. For example, they state that agricultural granules are designed to be applied dry, directly to the soil surface and not mixed with water; this may be true for some, but many solid agricultural pesticides are poured into either an applicator bin or a tank of water. Another claim, agricultural granules are made up of carrier particles (such as clay, corn cob, or sand) to which the active ingredient is sorbed, but most antimicrobial granules do not contain an inert carrier. This claim is true for some but not for agricultural dry flowables, and the difference should be accounted for by their aerodynamic diameters (if they differ) and the known concentrations of their AIs. Their other justifications can be questioned similarly.

In contrast to the Agency's approach, a more scientific focus would be based on the use conditions outlined above (see item 1) or on a few other parameters such as the range of AaiH, the size of the pouring containers, and the use or not of scoops. Further discussion revealed that there are more scientific-based differences between the new AHETF data and that proposed herein. The agricultural containers in AHE39 were all 10 and 13 lb. bags and only half of those in AHE80 are within the 1 to 100 lb range of those proposed herein;[10] agricultural mixer/loaders rarely if ever use scoops that all the occupational biocide handlers will use; only 10 of AHE39's 25 MEs have an AaiH of 100 lb. or less (the range of interest to the AEATF). Thus, a valid scientific basis was found for conducting the proposed studies. In the end, the results of at least a portion of the two studies should be compared, and their differences and similarities used to provide further quantitative insight into the effects of use conditions.

4. In addition to the statistical issue of incorporating a randomization structure (noted in the next to last paragraph in item 1), an additional word of caution was offered. The statistical analysis of the gathered data will include modeling exposure as a linear function of AaiH handled. If data are collected at only three levels of AaiH handled, the choice of alternative models will be severely limited and difficult, if even possible, to assess if the anticipated linear model is found to be inappropriate. The power for testing the assumptions of proportionality will be relatively low. A design that included more levels of AaiH handled and fewer, if any,

[10] However, the size of bags is not regulated.

replicates at a given level of AaiH would allow the functional relationship between exposure and AaiH handled to be more fully explored and would provide greater power for testing the assumption of proportionality.

5. The Board commented that the acute dermal irritation studies and acute eye irritation studies (Shah, 2013a), upon which several decisions regarding the safety of human subjects were made, were conducted in 1981 (33 years ago) before Good Laboratory Practices (GLPs) were required by EPA. The notes to those studies indicate "Study not performed to GLP and no guideline is stated, but meets basic principles of a guideline study" (Shah, 2013a, pp. 4 and 6). The Board recommended that the age and quality (in terms of compliance with GLPs) of research be explicitly considered when submitting toxicity studies in support of the safety of a chemical or agent.

Ethics

Charge to the Board

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

Board Response to the Charge

HSRB Recommendation

The Board concluded that the protocol submitted for review, if modified in accordance with EPA (Leighton, Sherman & Cohen, 2013) and the following HSRB recommendations, is likely to meet the applicable requirements of 40 CFR 26, subparts K and L.

HSRB Detailed Recommendations and Rationale

The submitted documents assert that the revised study will be conducted in accordance with the ethical and regulatory standards of 40 CFR 26, Subparts K and L, as well as the requirements the US EPA's GLP Standards described at 40 CFR 160 (Shah, 2013b, p. 12). FIFRA §12(a)(2)(P) also applies.

The study sponsors have submitted all required materials and documents to the EPA and HSRB for review. Prior to this, the protocol was reviewed and approved by an independent human subjects review committee, Schulman Associates IRB (SAIRB) of Sunrise, FL. SAIRB is fully accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP) and listed as active on the Office for Human Research Protections (OHRP) website (Reg. #IORG0000635).[11] Minutes of SAIRB meetings, a copy of their policies and procedures, and a list of IRB members were provided.

[11] OHRP is an office of the U.S. Department of Health and Human Services.

1. Except as noted below, the Board concurred with the conclusions and factual observations of the ethical strengths and weaknesses of the study, as detailed in the EPA's Ethics Review (Leighton, Sherman & Cohen, 2013, pp. 16-19). The proposed study is likely to meet the applicable ethical requirements for research involving human subjects, in accordance with the following criteria:

a. Risks to participants are commensurate with anticipated benefits to participants or society. Risks of study participation are six-fold: 1) allergic reaction or sensitivity to the test material; 2) allergic reaction or sensitivity to the surfactants used for hand and face/neck washing; 3) heat-related illness; 4) physical injury as a result of scripted activities; 5) psychological discomfort from undressing in the presence of a research technician; and 6) psychological stress and/or breach of confidentiality for pregnancy test results. These risks are minimized appropriately and are likely justified by the potential societal benefits, if the study is not duplicative of prior studies and produces useful data. There are no direct benefits to the participants.

- For the occupational portion of the study, only experienced handlers who are currently employed where they use powder or granule chemicals as part of their job and who consider themselves to be in good health will be enrolled. Similarly, for the consumer portion of the study, only participants who have experience handling and pouring powder or granular formulated pool maintenance chemicals and who consider themselves to be in good health will be recruited.
- The test material, cyanuric acid (1,3,5-triazine-2,4,6-triol), was chosen as a surrogate material because of its low toxicity and widespread use as a commonly used pool maintenance chemical. Current safety regulations do not require the use of gloves while pouring this product. While the Materials and Safety Data Sheet (MSDS) for cyanuric acid lists the use of chemical resistant gloves due to a potential for skin irritation, that reflects current industry practices that are meant purposefully to be overprotective, particularly for those working with large amounts of cyanuric acid in an occupational setting or those who have open cuts or sores on their hands. Participants with skin conditions or injuries to their hands (or face/neck) will be excluded.
- The study will exclude participants who have a history of sensitivity to the test material or to the surfactants used for the hand and face/neck washing. A Board member suggested adding a question to exclude persons with chronic respiratory illnesses or conditions.
- Subjects will be reminded about safe chemical handling practices and procedures, wearing appropriate PPE (including gloves in the occupational portion of the study), and will be monitored for any accidental or unintended product exposure of an extreme nature.
- Appropriate stopping measures are in place in the event of an injury or other adverse outcome.
- Risk of heat-related illness is minimized appropriately. Heat index will be monitored with an associated stopping rule. A medical professional will be on site to observe the workers and provide urgent care. Nearby medical facilities have been identified in case of emergency, and transportation to medical treatment will be provided, if needed.

- Minors and pregnant or lactating women are excluded from participation, with pregnancy either confirmed by over-the-counter pregnancy testing on the day of study or by opt-out. The potential stigma resulting from study exclusion due to pregnancy is appropriately minimized.

b. Voluntary and informed consent of all participants

- The Board respectfully disagrees with the Agency's conclusion that "no potential subjects are from a vulnerable population" (Leighton, Sherman & Cohen, 2013, p. 16). Rather, a better description is that the study is not actively recruiting participants that come from potentially vulnerable populations. There is a possibility that some participants in this study might be vulnerable, susceptible to coercion and undue influence. Despite this, the study protocol includes mechanisms designed to minimize coercive recruitment and enrollment.
- The informed consent materials, if changed as recommended by the EPA (Leighton, Sherman & Cohen, 2013) and by the HSRB below, will adequately inform the subjects of the risks, discomforts and benefits from participation and of their right to withdraw.
- Monetary compensation is not so high as to unduly influence participants.
- Faithful Spanish-language translations of the informed consent documents and recruitment materials were provided. Although there are minor concerns about the use of language in these document (including reading level), these are unlikely to interfere with the rights of non-English volunteers to give their voluntary and informed consent to participate in the study.

c. Equitable selection of study participants

- The study is designed to recruit an appropriately diverse population of participants who represent likely occupational and consumer (residential) users of the test material.
- The recruitment process has been carefully designed to assure that no subjects will be coerced or unduly induced into participating.

2. The Board recommended that the study protocol be modified to address the concerns noted in the EPA's Ethics Review (Leighton, Sherman & Cohen, 2013, pp. 16-19). In addition, the Board raised the following concerns:

a. The Board respectfully disagrees with the Agency's suggestion that the "Research-Related Injuries" section of the informed consent forms be revised to read as follows: "*If you experience an eye reaction, **skin reaction, respiratory irritation** or other adverse effect that you believe is related to your participation in the study, you should seek medical treatment and call the Study Director immediately at 1-877-298-7008*" (Leighton, Sherman & Cohen, 2013, p. 18). In fact, this revision does not go far enough. Study participants should be instructed to seek treatment and inform the Study Director of any eye reaction, skin reaction, respiratory irritation or other physical injury that occurs during or after participating in the study, regardless of whether or not the volunteer believes that it is related to the study.

b. It is not necessary or appropriate to state that cyanuric acid "does not require gloves or any other protective equipment to use" (Shah, 2013b, p. 31) on the occupational monitoring informed consent form. This may be confusing to participants, as they will be required to wear PPE during the study and will be given a copy of the MSDS to read, if requested. The study investigators should also consider how to handle the possibility that a participant in the consumer-monitoring phase of the study may ask to wear gloves.

c. Since study participants must self-report being in "good health," it should be clear what that term means. For example, since participants will be required to move 25-90 lbs. of product, some mention of those physical requirements should be made in reference to the health-related inclusion criterion.

d. With respect to the balance of risks and benefits, the submitted documents state that the risks of this study are "far lower than the risks of not being able to use effective antimicrobials for lack of information on the potential exposure to users" (Shah, 2013b, p. 26). This language includes assumptions about downstream consequences of decisions about conducting or not conducting specific research studies. The Board thus recommended that the study sponsor change this wording to read that "risks are reasonable in relation to the importance of understanding exposure patterns for consumers and occupational users of antimicrobials."

e. Participants in the study are allowed to take a short break if requested, either to use the bathroom or to have a cold drink. If the former, the researchers will conduct a hand wash to remove any product. Is the same true of the latter case, when a participant asks for a cold drink? Hand washes should also occur before any beverage consumption to reduce a participant's risk of accidental ingestion.

f. The study protocol should define the qualifications of the medical personnel needed and clarify this in the appropriate sections of the protocol.

g. The Board recommended that researchers complete a course in human subjects protections within three years of study initiation and completion.[12] Depending on when the study occurs, some investigators may exceed this recommended time limit.

A New Scenario Design and Associated Protocol from the AEATF-II Describing Proposed Research to Monitor Dermal and Inhalation Exposure During Application of Latex Paint Containing an Antimicrobial Pesticide Product Using Brush and Roller Equipment

Overview of the Scenario Design and Associated Protocol

The Antimicrobial Exposure Assessment Task Force (AEATF-II) proposes to measure dermal and inhalation exposures during the brush and roller application of interior latex paint, which contains an antimicrobial pesticide product (AEA09). The study participants will be recruited from the general (consumer) population, under the assumption that people who paint infrequently are more likely to experience greater exposures than professional painters.

[12] Within three years is generally considered "best practice" for training; e.g., see Section III D at http://mrmc.amedd.army.mil/assets/docs/orp/guidelinesForInvestigators.doc

The study will take place in a vacant building in Fresno, California. There will be 18 monitoring events (MEs), 6 for each of 3 chemical concentrations in the paint. The chemical to be used in this protocol is 1,2-Benzisothiazol-3(2H)-one (BIT). Study participants will apply about 2 gallons of paint using best-selling paint brushes and rollers. While opening and closing the paint can will be part of each ME, cleanup will not be included. Dermal exposures will be measured using inner and outer dosimeters, hand and face washes/wipes, and painter's hats. Additional exposures will be studied based on the results of gauze pads used to scrub participants' hands. During each ME, an OSHA Versatile Sampler (OVS) tube connected to a personal air sampling pump will be used to assess breathing zone inhalation exposures. Also, a three-stage Resp/Con Particle Sampler will be used to examine particles of 2.5, 10 and 100 µm.

The Agency plans to use the data from this study to estimate typical daily dermal and inhalation exposures among occupational and residential users of latex paint containing antimicrobial products, when applying them over a range of areas with a variety of paint rollers and brushes. The estimated exposures will be used to approximate risks to users of latex paint and similar products.

EPA's review of the proposed protocol was documented on March 14, 2014, and presented to the HSRB on April 8, 2014. The protocol was reviewed and conditionally approved by an independent human subjects review committee, Schulman Associates IRB (SAIRB) of Sunrise, FL.

Science

Charge to the Board

- Is this research likely to generate scientifically reliable data, useful for assessing the exposure of those who apply latex paint containing an antimicrobial pesticide using a brush or roller?

Board Response to the Charge

HSRB Recommendation

The Board agreed with the Agency's conclusion that, if modified according to Agency and HSRB recommendations, the proposed research to monitor dermal and inhalation exposure during application of latex paint containing an antimicrobial pesticide using brush and roller equipment is likely to produce scientifically reliable data. The Board also agreed that the modifications to the protocol suggested by the EPA (Leighton, Sherman & Cohen, 2014a, p. 2) be accomplished before initiation of the study.

HSRB Detailed Recommendations and Rationale

The Board made several recommendations, some bearing directly on the protocol for this study and others that should be considered for future studies of this nature.

1. Recommendations bearing directly on the protocol for this study

a. *Study design*: The Board recommended that the Agency reconsider the midpoint identified in this protocol. The middle concentration should be chosen to prevent high and low concentrations from having undue influence in fitting the regression to the data. Using only three dosage levels may not detect the true association between the dosage and exposure levels, and restricts the type of functions (such as quadratic and other complex lines) that can be fit to a straight line or a set of straight lines.. The HSRB recognized that adding more middle points could change the number of MEs but suggested that the Agency at least consider setting a midpoint that is more equidistant between the high and low concentrations.[13]

The study design uses what is termed "purposive diversity selection" as a means to assess the full range of variability by capturing many different activities/conditions in the fewest number of MEs (Shah, 2014a, p. 13). This is a good approach given the high cost of each monitoring event and limited sample size but the success of this approach depends on knowing in advance what factors have the greatest influence on variance in the outcome. The study identified three factors to achieve diversity: the date of application, the level of the active ingredient (AI) and the subject. The date of the application will likely have a relatively small contribution to variability. The level of AI in the paint is a controlled variable that clearly would influence the distribution of exposure (discussed above). The subject (careful or sloppy) is expected to have moderate influence on variance. These three factors are either purposively or randomly selected to achieve diversity in the outcome.

However, several other factors that potentially contribute to variance are discussed in the protocol including the roller and brush selection, wall finish, bucket size and the order that the monitoring events occur during the day. For example, if a subject participates in an ME that occurs in the morning versus late afternoon or on a Monday versus a Friday, this may contribute to variability just based on the scheduling. Additionally, the technicians monitoring the study may interact with the subjects differently for the same reason (how they feel at different times during the day or on different days of the week). These additional sources of variability are excluded by the purposive diversity selection. No justification is provided for why these other factors are standardized rather than being "purposively or randomly" included. Given that the primary exposure pathway for the brush and roller protocol is spatter and inadvertent contact with wet paint, factors such as roller nap thickness, paint type (density, sheen) and wall finish or texture could contribute significantly to variability in the outcome. Selecting the "best sellers" for painting tools can provide data representative of the central tendency but limits the range of the outcome. The HSRB recommended that either these additional factors be included in the purposive diversity selection process to "capture the range of exposure variation that is expected to exist" (Shah, 2014a, p. 7), or the statement that the protocol captures the range of variation be removed.

[13] Another approach would be to distribute the same number of MEs (18) over six equally spaced dosages, thus having only three MEs per point instead of six MEs for each of three points, as in the proposed protocol. Increasing the number of AI dosages from three to six could improve the chance of detecting the true dosage-exposure association and increase the precision of exposure data estimates. Furthermore, following blinded dosage assignments to 18 MEs would avoid any placebo effects associated with the exposure measurements.

b. *Statistical modeling:* The main objective of this exposure study is to estimate the following summary statistics for exposure values after testing and confirming the expected log-normal distribution and the proportionality assumptions.

- AM = Modeled arithmetic mean = exp(LnGM) exp(½ Variance)
- GM = Modeled geometric mean = exp(LnGM)
- GSD = Modeled geometric standard deviation = exp(SD)
- P95 = Modeled 95th percentile = exp(LnGM) exp(Z95×SD)

However, if the data collected from this study fail to confirm the log-normal and proportionality assumptions, then the estimated summary statistics under-estimate (depending on the degree of non-linearity) the exposure summary statistics reported above. Therefore, if the study data reveal that association between dosage and exposure levels are significantly non-linear, evaluating for other non-linear dosage-response models such as log-logistic models (https://support.sas.com/documentation/cdl/en/statug/63033/HTML/default/viewer.htm#statug_nlin_sect036.htm) and logistic models with 3 parameters (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2586183/pdf/nihms77514.pdf) are recommended for these exposure data. Also, the 95% confidence interval estimates for the arithmetic mean (P95) computed from the log-transformed data normally underestimate the error standard deviation, even after the back transformation.

Furthermore, as in similar studies, the Board encouraged the application of quantile regression models to estimate 95th percentile exposure estimates, in addition to reporting the arithmetic means.

Quantile regression methods model the relationship between dosage and the conditional quantiles of exposure; thus, it is especially useful in applications where extremes are important, such as in studies where upper quantiles of exposure levels are critical from a public health perspective (http://www2.sas.com/proceedings/sugi30/213-30.pdf).

c. *Exposure pathways:* The Brush and Roller protocol, as designed, focuses on non-volatile active ingredients in paints where the primary exposure pathway is physical contact with the paint through spatter, spills, and/or inadvertent contact with wet surfaces. The focus on non-volatile active ingredients was implied throughout the protocol and confirmed during the HSRB review meeting. This assumption can be verified with results from the personal air sampling during the ME. The protocol and justification for use of BIT (1,2-Benzisothiazol-3(2H)-one) should clearly define the "non- volatile" cutoff above which the current protocol will not be appropriate (*i.e.*, vapor pressures less than 0.1 mmHg). Otherwise, the assumption of a single representative surrogate of active ingredients breaks down because of the difference in physical chemical properties[14] which influence exposure pathways.

The protocol states that a painter's hat will be worn by all subjects and paint on the hat will be included in the characterization of whole body exposure. If the painter's hat is included as a surrogate surface, then a painter's sock/hood would be more representative. The shape of the hat and the brim on the hat change the contact area for exposure to spatter while a

[14] For example, vapor pressure, solubility, diffusivity and evaporation rate.

painter's sock/hood fits snug against the surface of the head with the added advantage of providing coverage on other parts of the face and neck (depending on how it is worn). Subjects are expected to wear their own socks and shoes. This could lead to an unanticipated expense to the subjects if they get paint on their shoes. Booties should be provided to prevent damage to subject's shoes, even if paint on the booties are not included as part of the external dosimeter.

d. *The test room design:* Test rooms for the Brush and Roller Protocol are designed to provide standardized conditions for the simulated painting events. *It is critical that these rooms be ventilated continuously during the MEs.* The protocol suggests turning off "ceiling ventilation fans" while ME is conducted (Shah, 2014b, p. 34). Exhaust fans should not be turned off during activity in the test rooms. Turning off fresh air ventilation during the MEs presents a real and unnecessary risk of symptoms related to exposure to bioeffluent (CO_2) and volatile constituents of the paint. California's Title 24 (California Energy Commission [CEC], 2008) and ASHRAE 62.2 (ASHRAE, 2013) both specify minimum required fresh air ventilation rates per occupant and/or unit floor area. The intent of both standards is to assure that the fresh air ventilation is sufficient to maintain acceptable indoor concentrations of occupant-generated pollutants – such as carbon dioxide – and acceptable indoor concentrations of pollutants emitted from building materials, furnishings, and the products used in buildings. The protocol should identify the appropriate minimum ventilation rate using either the CEC 2008 document or ASHRAE 2010 and design the test rooms to include an appropriately sized exhaust fan in each room to be operated continuously during the MEs. Given that the primary exposure pathway is expected to be physical contact with wet paint (spatter, spills and inadvertent contact), the fresh air ventilation is not expected to affect exposure to the antimicrobial surrogate. The exhausted air from the test room(s) should be vented outdoors.

e. *Additional test room issues:* Carryover of the surrogate antimicrobial chemical between experiments will be measured using both air samples collected in the rooms and surface wipes collected from the walls. It is unclear why the wall wipe samples are needed. If BIT is in the paint applied to the walls, and if the sampling method is effective, BIT will be detected in the wall wipes. The Board recommended that the protocol include some explanation of how these wall wipes will be used to understand exposures or define re-entry times because the exposure pathway for BIT in dry paint is not expected to contribute to the outcome.

The HSRB believes that industry data are available on typical drying times and/or re-entry times for painting; this information is expected to give a good estimate of how soon a room can be re-used for another ME. If this information is not available through industry partners, the protocol should include a verification task that characterizes the test rooms and the amount of time between experiments before re-use. This would entail painting the rooms with a finish coat of paint and monitoring room concentrations (not the user) over time to get a lucid understanding of clearance. That information can be used to determine how many test rooms are needed and the amount of time that should elapse between uses in each room.

The protocol should specify that the paint will be used in the consistency as received without further dilution.[15] The paint sheen should also be specified[16] because different sheen paints

[15] Note that if the paint is diluted it could increase the amount of spatter experienced during the ME.

could have different surface tensions resulting in different amounts of splatter for a given roller/brush/wall combination.

f. *Other comments:* The Board also noted that the study design seems to be based on the assumption that there will be a linear build-up of exposure by time. However, exposures will vary within the study period. There was concern that the measurements obtained will not reflect this variation and may not provide accurate exposure estimates. A member recommended that the Agency consider requiring measurements which will characterize exposure variations.

EPA has selected "best-selling" brushes and rollers for use in this study. Best selling items may be most representative, but they may not be the conservative choice since cheaper painting implements may drip more and lead to greater exposures. The Board recommended that the Agency clearly enumerate (and offer some rationale for) selection of both conservative and non-conservative factors embedded in the brush and roller study design.

Interpretation of the results of this study will be highly dependent upon results of a companion washing study (see review of AEA08 below). If the washing recovery study is not conducted in a scientifically sound manner, results of this study will not be useful. Therefore, this proposed protocol should not be approved or implemented until the companion washing study has been successfully implemented.

2. Recommendations for future studies of this nature

a. *Dermal No Observable Adverse Effects Levels (NOAELs)* or other toxicity parameters are routinely cited in evaluation of protocols that involve dermal exposure. The values are typically drawn from studies submitted in support of registration that are not generally available to HSRB members (except by FOIA processes that cannot be accommodated by the HSRB review timetable). Hence, the dermal toxicity study details are unknown. Traditionally, inadequate consideration has been given to the kinetics of dermal absorption in the design and conduct of dermal toxicity studies. Dermal absorption may be either flux or supply limited (Kissel, 2011). In the case of flux limitation, increasing skin loading will not produce an increase in absorbed dose; therefore, apparently increasing NOAELs will be misleading. Since the credibility of dermal toxicity values cannot be fairly evaluated in the absence of knowledge of experimental conditions, critical experimental details should be routinely provided in addition to toxicity outcomes.

b. *Worst case scenario:* There are no known data indicating whether consumer applicators (users) or professional applicators will get more paint on their skin. Thus, the justification for using consumer painters as a worse-case scenario is not supported by evidence. Among the justifications for using consumers is the statement within the Science and Ethics Review (Leighton, Sherman & Cohen, 2014a, p. 4[17]): *"This focus on consumer applicators is considered the more conservative approach, given that consumer painters are expected to be less skilled than professional painters. A less skilled painter is more likely to expose*

[16] The Board observed that the MSDS and the label in the protocol do not agree.

[17] Based on Shah, 2014a, p. 9.

themselves to the drips and paint spills."[18] An alternative opinion[19] is that professional painters are less concerned with personal contact with paint than are typical consumers, *i.e.*, they allow more paint to get on (and perhaps stay on) themselves. The lack of justification for using only consumer painters does not detract from the data's scientific reliability but is a weakness when extrapolating exposure measurements to professionals.

Ethics

Charge to the Board

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

Board Response to the Charge

HSRB Recommendation

The documents submitted to the EPA and the HSRB do not fully meet the regulatory requirements. However, the Board concluded that the protocol submitted for review will likely meet the applicable requirements of 40 CFR part 26, subparts K and L, if: 1) it is modified in accordance with EPA (Leighton, Sherman, & Cohen, 2014a) and HSRB recommendations; 2) necessary approvals are obtained; and 3) additional documents are provided to the Agency for review.

HSRB Detailed Recommendations and Rationale

The submitted documents indicate that the revised study will be conducted in accordance with the ethical and regulatory standards of 40 CFR 26, Subparts K and L, as well as the requirements the US EPA's FIFRA GLP Standards described at 40 CFR 160, and the California State EPA Department of Pesticide Regulation study monitoring (California Code of Regulations Title 3, Section 6710) (Testman, 2014, p. 48). FIFRA §12(a)(2)(P) also applies.

The protocol was reviewed by an independent human subjects review committee, Schulman Associates IRB (SAIRB) of Sunrise, FL, prior to submission. SAIRB is fully accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP). SAIRB is listed as an active IRB on the OHRP website (Reg. #IORG0000635). Minutes of SAIRB's meetings and a copy of SAIRB's policies and procedures were provided to the Agency. These documents indicate that SAIRB reviewed this protocol pursuant to the standards of the Common Rule (45 CFR Part 46, Subpart A).

However, at the time of the HSRB meeting, SAIRB had granted only "conditional approval" for the study, with full approval contingent upon review by the California Department of Pesticide

[18] Similar statements such as "*e.g.*, a slow fastidious painter may contact less paint than someone who is careless and sloppy" are also made (Leighton, Sherman, and Cohen, 2014a, p. 7).
[19] Based on the adage that "familiarity breeds complacency," regarded as folklore in occupational health professions.

Regulation (CDPR), EPA and this HSRB. Documents provided by SAIRB reflect only this conditional approval. Thus, the study sponsor was not in compliance with the requirements of 40 CFR 26.1125, which requires submission of "Official notification to the sponsor or investigator, in accordance with the requirements of this subpart, that research involving human subjects has been reviewed and approved by an IRB." Submission of meeting minutes from SAIRB, documenting final approval and attendance are still required, together with documentation of IRB members' relationship with the study's sponsor.

As the study will take place in California, Title 3, Section 6710 of California's Code of Regulations also require review and approval by CDPR. Copies of communications between the study sponsor and CDPR and a copy of that department's approval were provided.

Except as noted below, the Board agreed with the conclusions and factual observations of the ethical strengths and weaknesses of the study, as detailed in the EPA's Ethics Review (Leighton, Sherman & Cohen, 2014a). The proposed study is likely to meet the applicable ethical requirements for research involving human subjects, in accordance with the following criteria:

a. Risks to participants are commensurate with anticipated benefits to participants or society. Six risks of study participation are identified by the HSRB reviewers: 1) reaction to latex paint or the active ingredient BIT that it contains; 2) discomfort from clothing and air pumps worn during the study; 3) irritation from alcohol wash and wipes; 4) heat stress from doing physical work while wearing two layers of clothing and a hat; 5) embarrassment from changing clothes in the presence of a researcher; and 6) surprise, embarrassment, or psychological stress from pregnancy testing and/or breach of confidentiality for pregnancy test results. These risks are minimized appropriately, are characterized as of low probability, and are justified by the potential societal benefits associated with data on dermal and inhalation exposure during application of latex paint containing BIT (1,2-Benzisothiazol-3(2H)-one), using a brush and roller. There are no direct benefits to the participants.

    - The test material, BIT, is an EPA-registered pesticide that is used in many household products including paint, laundry detergents, and household cleaners. Although it is considered to be moderately toxic by oral and dermal routes, a slight dermal irritant, and a moderate dermal sensitizer, for the purposes of this study it will be used in a latex paint formulation that is commercially available and in a manner that is consistent with the requirements of the EPA-approved label. Based on toxicological data currently available for BIT, coupled with appropriate exclusion criteria, and personal protective equipment, study participants are unlikely to be at risk of adverse side effects with exposure.
    - The study will exclude participants who have a history of sensitivity to the test material, latex or latex paint, or isopropyl alcohol. Subjects who report themselves to be in poor health or who have broken skin on the hands will also be excluded. Additional exclusion criteria, the justification for which is not explained and which may or may not be appropriate, include: severe respiratory disorders (*e.g.*, moderate or severe asthma, emphysema); cardiovascular disease (*e.g.*, history of myocardial infarcts, stroke, congestive heart failure, or uncontrolled high blood pressure); severe diabetes; or immunological suppression (e.g. undergoing chemotherapy, transplant patients).

- Appropriate stopping measures are in place in the event of an injury or other adverse outcome.
- Minors and pregnant or lactating women are excluded from taking part. Pregnancy is either confirmed by over-the-counter pregnancy testing on the day of study or by opt-out. Only volunteers whose test results show them to be non-pregnant will be allowed to participate. Potential stigma resulting from exclusion due to pregnancy is appropriately minimized. Testing is done in private and with the option of discrete withdrawal. Information regarding pregnancy test results will be kept confidential.

b. Voluntary and informed consent of all participants

- The Board respectfully disagrees with the Agency's conclusion that "no potential subjects are from a vulnerable population" (Leighton, Sherman & Cohen, 2014a, p. 11). Rather, a better description is that the study is not actively recruiting participants that come from potentially vulnerable populations. There is a possibility that some participants in this study might be vulnerable, susceptible to coercion and undue influence. The study protocol, however, includes several mechanisms designed to minimize coercive recruitment and enrollment.
- Research participants will be recruited through advertisements in English and Spanish in three local newspapers that will be seen by a diverse population of consumers likely to use the product, instead of in a workplace setting where there is potential for coercion or undue influence from an employer.
- The informed consent materials, if modified as recommended by the EPA (Leighton, Sherman & Cohen, 2014a) and the HSRB below, will adequately inform the subjects of the risks, discomforts and benefits from participation, and of their right to withdraw.
- Spanish translations of the informed consent documents and recruitment materials *were not provided*. The study sponsors have indicated that they will have these documents translated once SAIRB has fully approved the study. These documents must be submitted to EPA before the HSRB can confidently recommend that the protocol will likely meet the applicable requirements of 40 CFR part 26, subparts K and L. Additionally, SAIRB's Standing Operating Procedures do not include a description of how translated documents are validated; documentation of the process of validation should be provided to the Agency along with the translated materials.
- Monetary compensation is not so high as to unduly influence participants.

c. Equitable selection of study participants

- The protocol is designed to recruit participants from an appropriately diverse population who represent likely personal or commercial users of the test material.
- The recruitment process has been designed to assure that no subjects will be coerced or unduly induced into participating. However, recruitment through advertisements placed exclusively in local print media will draw literate subjects who may not represent the population of less-educated consumers who may use latex paint without reading the directions.

1. The Board recommended that the study protocol be modified to address the concerns noted in the EPA's Ethics Review (Leighton, Sherman & Cohen, 2014a), with one minor exception noted below:

a. EPA's Ethics Review called for the study's exclusions to be expanded from candidates known to be allergic to latex paint, soaps, or isopropyl alcohol "*to also exclude individuals who have allergies or sensitivities to BIT or other chemical-based products.*" The Board recommended the phrase "chemical-based products" be changed to "chemical products."

In addition, the Board raised the following concerns:

b. The HSRB respectfully disagrees with the statement that, "there is little incremental risk associated with [the study]" (Testman, 2014, p. 13). Despite the fact that the test materials are of low toxicity and that pesticide exposures are potentially higher during normal residential or commercial painting activities, there nevertheless is a risk associated with BIT exposure that would otherwise not exist outside of this intentional exposure study.

c. The provision for a researcher *of the same sex as the participant* being present when the participant changes clothes, while intended to minimize the potential embarrassment of being observed, may not have the intended effect for all participants. The research team should consider offering the participant a choice of researchers to observe them changing clothes.

d. In its description of the study, the protocol intermittently uses the term "applicators" to refer to the subjects who will be applying latex paint to walls and ceilings with brushes and rollers. The Board noted that the term "applicator" means an implement, such as a brush or roller, and recommended that subjects be referred to as "appliers" if specific reference to their role in applying paint is necessary.

e. The HSRB recommended that the consent form and protocol be modified as follows:

- Since study participants must self-report being in "good health," clear definitions of these terms should be in the protocol and in the informed consent document. Some of the exclusion criteria – severe respiratory disorders, cardiovascular disease, severe diabetes and immunological suppression – seem inappropriate given the physical requirements and risks of the study. Justification for these criteria should be provided, or the exclusion criteria revised. If these are appropriate exclusion criteria, ensuring that potential participants qualify for the study will require investigators to ask somewhat invasive questions about personal health status and medical history. The "Subject Invitation to Participate" script should thus include mention of these exclusion criteria, and the study enrollment section of the informed consent document should be revised to reflect the various exclusion criteria rather than simply state "we will ask you about your general health" (Testman, 2014, p. 63).

- *Study Procedures Point 10* on the consent form states that the researchers "may take pictures or video to show what happened in the study but those pictures will not show faces or tattoos in the final report" (Testman, 2014, p. 65). The Board recommended that

the phrase "faces or tattoos" be expanded to "faces, ears, tattoos, or other identifying features".

- *Study Procedures Point 12* on the consent form states that "The researcher will remove the painter's hat, air sampling pumps, and equipment" (Testman, 2014, p. 65). The words "from you" should be added to the end of this sentence. ("The researcher will remove the painter's hat, air sampling pumps, and equipment from you.")

- *Risks Point 1* on the consent form states "…if you think you may have gotten some of the paint in your eye…" (Testman, 2014, p. 66). The word "some" in this sentence should be replaced with the word "any".

- The last sentence of *Costs and Payment* states "…whether or not you are actually tested" (Testman, 2014, p. 68). The subject is not *tested*; the subject *participates in the test*. This phrase should be changed to "whether or not you actually take part."

- The last sentence of the first paragraph of *Confidentiality* states "any pictures of you in a report of this study will not show your face" (Testman, 2014, p. 68). This sentence should be expanded to "…will not show your face or other identifying features (such as piercings or tattoos)."

f. The HSRB recommended that researchers complete a course in human subjects protections within three years of study initiation and completion. Some investigators have or will (depending on when the study occurs) exceed this recommended time limit.

A New Protocol from the AEATF-II Describing Proposed Research to Measure the Removal Efficiency of 1,2-Benzisothiazol-3(2H)-one (Known as BIT) from Hand Surfaces Using an Isopropyl Alcohol/Water Wipes and Wash Procedure

Overview of the Proposed Protocol

The proposed removal efficiency study is pivotal to the conduct of the BIT exposure study (AEA09) reviewed above. The roller and brush latex paint study cannot proceed until this removal efficiency study (**AEA08**) has been carried out and the removal efficiency of BIT is considered to be adequate.

The proposed study is intended to assess the efficiency of a hand wash removal methodology; the method will then be used to monitor exposures of subjects after they apply a latex paint containing an antimicrobial (BIT), utilizing commercially available brushes and/or rollers. The AEATF II has stated that the primary objective of this study is to determine the removal efficiency of BIT in latex paint and in isopropyl alcohol (IPA) from human hands**.**

Study participants will be recruited from the general population of Fresno County, CA, and the surrounding area. Twenty-eight subjects will be qualified for the study; 8 will serve as alternates. Twenty individuals will be equally but randomly assigned to one of four study groups: two concentrations of BIT in latex paint and two concentrations of BIT in IPA.

The test subjects will have BIT-treated paint or BIT painted IPA applied to the surface of their right and left palms. The test substance will be allowed to dry on the subjects' hands for 45 minutes**;** the researchers will then perform a hand wash procedure similar to the hand wash procedure in the painting study (AEA09). The results of the paint portion of the efficiency study will be used to correct for any losses on the subjects' hands in the paint brush/roller exposure study. The results of the IPA portion of the efficiency study will be used to compare the differences in the efficiency between paint and a non-paint liquid. The IPA portion will also be available for future studies using non-paint liquids for hand wash sampling method corrections.

The Agency's review of the proposed protocol was completed on March 18, 2014, and presented to the HSRB on April 8, 2014. The protocol was reviewed and approved by an independent human subjects review committee, Shulman Associates IRB (SAIRB) of Sunrise, FL. The Agency made recommendations for improvements in both scientific and ethics aspects of the protocol.

Science

Charge to the Board

- Is this research likely to generate scientifically reliable data, useful for determining the removal efficiency of BIT from the hands due to dermal exposure associated with the use of latex paint and non-paint liquid solutions containing BIT?

Board Response to the Charge

HSRB Recommendation

- With the exception of one member, the Board concluded that the proposed research is likely to generate scientifically reliable data, useful for determining the removal efficiency of BIT from the hands due to dermal exposure associated with the use of latex paint and non-paint liquid solutions containing BIT, provided that the protocol is modified to address the issues raised by EPA and the HSRB.

HSRB Detailed Recommendations and Rationale

The Board carefully reviewed the protocol and determined that a number of methodological issues merit further attention and modification to ensure that the results of the study are useful for estimating exposure to BIT when present in commercial latex paints.

The HSRB noted that the sponsor proposed to apply BIT – either in paint or in IPA – to the palmar region of the hands, utilizing a glass capillary tube to spread the test material (paint or IPA). The Board expressed several concerns about this approach.

1. The HSRB was concerned that laboratory capillary tubes are rather fragile and typically have sharp ends. Even if the ends were heated and sealed, the Board remained concerned with the likely breakage of the glass tubes while the application of the test material was taking place.

2. Based on the information provided (Leighton, Sherman & Cohen, 2014b, pp. 4, 5 and 8), the proposed loading of paint (mL/cm2) appears to be excessive for many people's hands.[20] Reported dimensions for the human palm depend upon how they are defined and measured, but 8 × 10 cm (80 cm2) might be an average.[21] Noting that the test substance is not to be applied within a 2 cm edge around the palm that leaves a total area of approximately 4 × 6 cm or 24 cm2 for application of test material, approximately half of the 50 cm2 palm surface area estimated by the EPA reviewer.

3. Applying 500 µL (0.5 cm3) of latex paint to 24 cm2 (20 µL/cm2) will yield a layer of paint about 2 mm thick (or 1 mm thick to 50 cm2). This seems to be well in excess of the thickness expected of accidental paint blotches, smears, and small drops or spatter landing on the hands, face, or neck. Moreover, large deposits of that thickness are likely to be wiped (in fact, personal experience suggests that a 2 mm deposit thickness on a near-vertical skin surface if left unattended, is likely to ooze and potentially to drip). The 0.04 mm thick layer that would result from applying 100 µL (0.1 cm3) of BIT in IPA to 25 cm2 of skin (4 µL/cm2) seems at first glance to be less of a concern, but IPA's much lower viscosity could result in the same dripping unless the subject keeps the palms of their hands upright and horizontal.

Unfortunately, for users of recovery data, the effect of the thickness of the deposit in the real world can have a greater effect on recovery efficiency than the BIT concentration.[22] If one considers the process of adsorption and absorption on a molecular level, for molecules to contact the skin, they must be within some small distance (somewhat like a boundary layer) determined by the diffusion rate of the chemical within the deposit and residence time on the skin. In a high viscosity deposit (*e.g.*, paint or (in the extreme) detritus in a field setting), diffusion will be primarily molecular (versus convective diffusion), and such intermolecular processes occur over distances on the order of nm, not µm. Thus, the number of molecules (*i.e.*, the mass of the chemical) that will reach the skin will be proportionate to concentration within the deposit and to the thickness of the deposit, only if the thickness is less than the depth of such a pseudo-boundary layer. Molecules in a paint layer beyond such a pseudo-boundary layer will have no effect on skin retention or recovery. The same mechanisms will apply to IPA only at slightly larger distances in inverse proportion to its lower viscosity. In addition, the effects of convection and adherence of IPA to the skin would be increased if the subject were to move their hands enough to cause some flow along the skin. This leads to the suggestion that paint thickness beyond some limit (perhaps as small as 0.05 µm) will have no effect on chemical retention by the skin, and any additional paint applied to the skin beyond such a thickness will result in disproportionately higher recovery rates when the supporting paint matrix is removed. Note that 0.05 µm is $> 10^{-4}$ less than the calculated 2 mm think layer of paint in the proposed protocol and still $> 10^{-2}$ less than the calculated 0.04 mm think layer of IPA. Thus, the results of measuring recovery at a paint loading in the range of 20 µL/cm^2 seems likely to over-estimate the recovery at much lower levels of loading in the planned brush, roller, and later spray studies.

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[20] The same concern may also apply, but to a lesser extent, to IPA.

[21] *E.g.* , see http://www.theaveragebody.com/average_hand_size.php, http://en.wikipedia.org/wiki/Hand and/or http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2938623/

[22] The agency is referred to the Transmittal of Meeting Minutes of the FIFRA Scientific Advisory Panel Meeting Held January 9 - 12, 2007 on the Review of Worker Exposure Assessment Methods.

4. It is important to recall that the palm of the hand is known to have among the lowest dermal permeability of any part of the body (Maibach, *et al.*, 1971; Wester, *et al.*, 1984; Baynes & Hodgson, 2004; Wester & Maibach, 2005). This knowledge suggests that limiting the recovery study to just the palm will bias the results toward a higher percent recovery. In addition, the palm is relatively smooth and easy to clean, which would also bias recovery results upwards. The Board recommended that dosing all or most of the entire hand be considered before the study design is finalized.

5. In addition to reasons to be concerned about the proposed total matrix volume in the washing study, there are also reasons to be concerned about the amount of AI to be employed. The washing study loads were selected to roughly match BIT skin loads in the brush and roller study anticipated to be roughly 1-10 µg/cm^2 based on a Pesticide Handler Exposure Database (PHED) painting study conducted with an unknown agent, which produced skin loads averaging 10.5 µg/cm^2 (Leighton, Sherman & Cohen, 2014b, p.4). EPA suggests that if actual loads in the washing protocol are a little lower, recoveries will be conservative in comparison to the brush and roller protocol. However, the 10.5 µg/cm^2 loading in the PHED painting study was achieved using paint containing 10,000 ppm of the target agent. BIT will be present in the brush and roller study paint at much lower levels, which suggests that loads will probably be much lower than the wash study design loads. This would lead to an expectation that the wash study recoveries will overestimate the brush and roller study recoveries, which could in turn lead to underestimation of exposures in the brush and roller study.

The Agency's attribution to Brouwer et al (2000) of "decreased removal efficiencies for low skin loadings" is consistent with the above logic (Leighton, Sherman & Cohen, 2014b, p. 8). However, the subsequent conclusion of the EPA review is that *"this [referring to a lower skin loading of 1.6 to 7.8 µg/cm^2 in this BIT proposal compared to 4.8 to 19.7 µg/cm^2 of BIT in the unreferenced research] would lead to a more conservative (protective) correction factor rather than less"* (Leighton, Sherman & Cohen, 2014b, p. 8) would only be true within certain constraints which probably are not true for this study.[23] The submitted protocol proposes to apply a skin loading of BIT lower than in the PHED paint study, but in a much thicker layer than was probably true for the rat study (not provided to the HSRB; see Boatwright, 2014, p. 91; Leighton, Sherman & Cohen, 2014b, p. 8)[24] and thicker than naturally occurs to painters. Therefore, in this study there will be less BIT actually reaching the skin, more BIT being recovered, and a less conservative protection factor than if a much lower loading of paint were tested.

Based on these points, the Board's recommendation is to test the recovery after applying the thinnest layer feasible based on the expected recovered dose and detection threshold. Second, it may be appropriate to keep the applied layer reasonably constant among subjects by varying the amount applied in proportion to the size of each person's palm area.

The desire for each subject to have a reasonably constant layer of paint is probably of less significance but was triggered by a series of statements near the top of p. 8 of Leighton, Sherman & Cohen (2014b) describing dermal absorption data in rats (MRID 46327901) and culminating

[23] The "probably" is needed because the Board was not given much information on the conditions of the prior BIT recovery study in PHED.
[24] Also, referred to in Boatwright, 2014, p. 91.

in *"This would imply that the 45 minute residence time proposed would be sufficiently long to allow the paint to dry yet not be substantially affected by dermal absorption over the anticipated 2 to 3 hour exposure time in the painting study."* The concern is that "substantially" could be viewed as misleading. An analysis of the reported data on rats shows that dermal absorption is fairly constant over the 72 hours at approximately 0.6±0.2%/hr (Boatright, 2014, p. 91). However, the results of the proposed recovery study will depend upon the combined effects of absorption and adsorption, and the adsorption data appear to follow first-order exponential kinetic equations with a half-life of about 10 hours.[25] So, if the resulting loading and recovery in the proposed study turn out to be the same as for this rat data, four times as much BIT would stay on or in the skin after 3 hours than after 45 minutes (about 11% versus 3%) which may be a *substantial* difference; the corresponding expected recoveries are 89% after 3 hours and 97% after 45 minutes.

A margin of exposure (MOE) for dermal exposure is reported based on a Lowest Observable Adverse Effect Level (LOAEL) from a 90-day rat study not available to the HSRB (Leighton, Sherman & Cohen, 2014b, p. 30). Hence, details (*e.g.*, vehicle, load, skin area exposed) of the dermal toxicity study are not available. Traditionally, inadequate consideration has been given to the kinetics of dermal absorption in the design and conduct of dermal toxicity studies. Dermal absorption may be either flux or supply limited (Kissel, 2011). In the case of flux limitation, increasing skin loading will not produce an increase in absorbed dose, and apparently increasing LOAELs or other toxicity parameters will be misleading. Since the credibility of dermal toxicity values cannot be fairly evaluated in the absence of knowledge of experimental conditions, critical experimental details should be routinely provided in addition to toxicity outcomes.

The extent of wetting will affect the degree of incapacitation that subjects experience for 45 minutes while the test substance is drying and the use of their hands will be at least limited if not denied. Clearly subjects should be instructed to take care of normal physiological needs before they get their hands wet.[26] The Board opined that it might be useful to carry out a small pilot test with simple, non-toxic, household items to better assess practical aspects of the proposal.

The Board was also concerned about the expectation that volunteers would be required to sit very still, with palms fully open and facing up for a period of 45 minutes following application of the test material to their palms to allow for drying before any washing occurred. The Board is of the view that trying to keep one's hand open for 45 minutes can become uncomfortable. The Board recommended providing the subjects with a simple tool (such as a brace) to help them keep their palms open; the form of an acceptable tool will be affected by the extent of the hand's surface that is wetted. The Board was concerned that compliance could be variable and poor.

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[25] The generic form of a model predicting skin retention is the sum of the linear absorption rate and exponential adsorption rate, as shown below. Recovery would be 1 minus retention.

$$\text{Retention} = [\text{avg. absorption rate} \times \text{time}] + [\text{final adsorbed fraction} \times (1 - e^{-\text{time/time coef}})]$$

The fit of the data provided within Leighton, Sherman & Cohen, 2014b, p. 8 yields the following coefficients that were used to anticipate the effects after 45 minutes and 3 hours.

$$\text{Retention} = [0.58\% \times \text{hours}] + [0.49\% \times (1 - e^{-\text{hours}/15})]$$

[26] Even something as simple as scratching an itch may not be allowed if their entire hand is wetted; leaving one or more finger tips untreated would be desirable but may not feasible.

The Board advised that better coordination is needed between the paint field exposure study and the laboratory BIT recovery study to assure that both studies use the same skin manipulation technique regarding scrubbing with gauze pads and rinsing (the procedure in the latter wherein "the subject rub[s] their fingers and palm together" (Leighton, Sherman & Cohen, 2014b, p. 4[27]), is not at all similar to the procedure utilized in the recovery efficiency study).

The HSRB noted that statistical issues, such as sample size and randomization, might need to be re-considered when developing a revised protocol that includes removal efficiency from both hands simultaneously (as in the painting study), rather than from the palms of two separate hands (as in the originally proposed efficiency removal study).

Although no hypothesis is stated explicitly, at least three are implied: (1) the removal efficiency for the dominant hand will be independent of that for the non-dominant hand. (2) the removal efficiency of BIT in latex paint will be the same as the removal efficiency of BIT in isopropyl alcohol. (3) BIT removal efficiencies will be the same at both BIT in latex paint concentration levels (120 and 600 ppm). If the first hypothesis is not true, then the subsequent analysis could have substantially less power than anticipated under the current design. If the third hypothesis is true, then data collected at 120 ppm would be combined with that collected at 600 ppm, and a correlation between the observations from the two hands would negatively impact the power.

An alternative approach would be to, for a given concentration, randomize BIT in latex paint to either the dominant or non-dominant hand and to use BIT in isopropyl alcohol at the same concentration on the other hand. This would be a split-plot design with concentration being the main unit treatment and latex paint/isopropyl alcohol being the subunit treatment. This would ensure independence between the observations made at 120 and 600 ppm, but still allow the third hypothesis to be tested. The foregoing statistical comments presume that each hand is treated separately. If a volunteer's two hands are treated as a single experimental unit, then other statistical considerations may be necessary.

Ethics

Charge to the Board

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

Board Response to the Charge

HSRB Recommendation

The documents submitted to the EPA and the HSRB do not fully meet the regulatory requirements. Despite this, the Board concluded that this protocol will likely meet the applicable requirements of 40 CFR 26, subparts K and L if: 1) it is modified in accordance with EPA (Leighton, Sherman & Cohen, 2014b) and HSRB recommendations; 2) necessary approvals are obtained; and 3) additional documents are provided to the Agency for review.

[27] Also, cited in Boatwright, 2014, p. 19.

HSRB Detailed Recommendations and Rationale

The submitted documents assert that the revised study will be conducted in accordance with the ethical and regulatory standards of 40 CFR 26, Subparts K and L, as well as the requirements the US EPA's GLP Standards described at 40 CFR 160 (Boatwright, 2014, p. 8). FIFRA §12(a)(2)(P) also applies.

An independent human subjects review committee, SAIRB of Sunrise, FL, reviewed the protocol prior to submission. Minutes of SAIRB meetings, a copy of their policies and procedures, and a list of IRB members were provided. SAIRB is fully accredited by AAHRPP and listed as active by OHRP (Reg. #IORG0000635). At the time of the HSRM meeting, SAIRB had only granted 'conditional approval' for the study, with full approval contingent upon review by the California Department of Pesticide Regulation (CDPR), EPA and HSRB. Because of this, the study sponsor was not in compliance with the requirements of 40 CFR 26.1125, which requires submission of "Official notification to the sponsor or investigator, in accordance with the requirements of this subpart, that research involving human subjects has been reviewed and approved by an IRB."

As the study will take place in California, Title 3, Section 6710 of California's Code of Regulations also require review and approval by CDPR. Copies of communications between the study sponsor and CDPR, and a copy of that department's approval were provided.

1. Except as noted below, the Board agreed with the conclusions and factual observations of the ethical strengths and weaknesses of the study, as detailed in the EPA's Ethics Review (Leighton, Sherman & Cohen, 2014b). The proposed study is likely to meet the applicable ethical requirements for research involving human subjects, in accordance with the following criteria:

a. Risks to participants are commensurate with anticipated benefits to participants or society. Risks of study participation, as determined by the HSRB reviewers, are six-fold: 1) allergic reaction or sensitivity to the test material; 2) allergic reaction or sensitivity to the latex paint; 3) allergic reaction or sensitivity to the isopropyl alcohol used for BIT (1,2-Benzisothiazol-3(2H)-one) application and hand washing; 4) injury that occurs during application of test material using a glass capillary tube; 5) irritation from rubbing the skin during the hand washing procedure; and 6) psychological stress and/or breach of confidentiality for pregnancy test results. These risks are minimized appropriately and are justified by the potential societal benefits. There are no direct benefits to the participants.

    - The test material, BIT, is an EPA-registered pesticide that is used in many household products including paint, laundry detergents, and household cleaners. Although it is considered to be moderately toxic by oral and dermal routes, a slight dermal irritant, and a moderate dermal sensitizer, for the purposes of this study it will be used in a latex paint formulation that is commercially available and in a manner that is consistent with the requirements of the EPA-approved label.
    - The study will exclude participants who have a history of sensitivity to the test material, latex or latex paint, or isopropyl alcohol. Subjects who are in poor health (by self-report) or who have broken skin on the hands will also be excluded. Additional exclusion criteria, which may or may not be appropriate, include: severe respiratory disorders (*e.g.*,

moderate or severe asthma, emphysema); cardiovascular disease (*e.g.*, history of myocardial infarcts, stroke, congestive heart failure, or uncontrolled high blood pressure); severe diabetes; or immunological suppression (e.g. undergoing chemotherapy, transplant patients).

- Appropriate stopping measures are in place in the event of an injury or other adverse outcome.
- Hand irritation from the washing procedure, if it occurs, is likely to be minor and easily treated with over-the-counter medications.
- Minors and pregnant or lactating women are excluded from participation, with pregnancy either confirmed by over-the-counter pregnancy testing on the day of study or by opt-out. The potential stigma resulting from study exclusion due to pregnancy is appropriately minimized.

b. Voluntary and informed consent of all participants

- The Board respectfully disagrees with the Agency's conclusion that "no potential subjects are from a vulnerable population" (Leighton, Sherman & Cohen, 2014b, p. 11). Rather, a better description is that the study is not actively recruiting participants that come from potentially vulnerable populations. There is a possibility that some participants in this study might be vulnerable, susceptible to coercion and undue influence. Despite this, the study protocol includes several mechanisms designed to minimize coercive recruitment and enrollment.
- The informed consent materials, if changed as recommended by the EPA (Leighton, Sherman & Cohen, 2014b) and by the HSRB below, will adequately inform the subjects of the risks, discomforts and benefits from participation, and of their right to withdraw.
- Monetary compensation is not so high as to unduly influence participants.
- Spanish translations of the informed consent documents and recruitment materials *were not provided*. The study sponsors have indicated that they will translate the informed consent documents and requirement materials once full approval of SAIRB is obtained.

c. Equitable selection of study participants

Although the protocol does not specify painting experience as an eligibility criterion, the EPA review states that "the test subjects will be drawn from the same populations as the painting exposure study" (Leighton, Sherman & Cohen, 2014b, p. 22).

- The recruitment process has been carefully designed to assure that no subjects will be coerced or unduly induced into participating.

2. The Board recommended that the study protocol be modified to address the concerns noted in the EPA's Ethics Review (Leighton, Sherman & Cohen, 2014b). Additionally, the Board raised the following concerns:

a. The HSRB recommended that the investigators not state that, "there is little incremental risk associated with [the study]" (Boatwright, 2014, p. 11). Despite the fact that the test materials are of low toxicity and that pesticide exposures are potentially higher during normal

residential or commercial painting activities, there nevertheless is a risk associated with BIT exposure that would otherwise not exist outside of this intentional exposure study.

b. Since study participants must self-report being in "good health," clear definitions of these terms need to be in the protocol and in the informed consent document.

c. The HSRB recommended that the informed consent document mention the potential discomfort that study participants might experience while sitting upright, arms on a table with palms up, for 45 minutes, together with steps that will be taken to minimize such potential discomfort.

d. Some of the exclusion criteria – severe respiratory disorders, cardiovascular disease, severe diabetes and immunological suppression – seem inappropriate given the physical requirements and risks of the study. Justification for these criteria should be provided, or the exclusion criteria revised. If these are appropriate exclusion criteria, ensuring that potential participants qualify for the study will require investigators to have clear definitions (*e.g.*, "broken skin") and ask somewhat invasive questions about personal health status and medical history. The "Subject Invitation to Participate" script should thus include mention of these exclusion criteria, and the study enrollment section of the informed consent document should be revised to reflect the various exclusion criteria rather than simply state "we will ask you about your general health" (Boatwright, 2014, p. 48).

e. The investigators will apply and spread the BIT/paint or BIT/IPA mixture using a glass capillary tube. These tubes can have rather rough ends or may shatter, potentially causing injury to the palms of study participants. This risk should be noted in the protocol and informed consent document. Alternatively, the investigators may want to consider alternate means of applying and spreading the test material that do not pose the same risk of injury.

f. The Board recommended that researchers complete a course in human subjects protections within three years of study initiation and completion. Some investigators have or will (depending on when the study occurs) exceed this recommended time limit.

A New Protocol from the U.S. Department of Agriculture Describing Proposed Research to Determine the Bite Protection Level of Repellent Treated Clothing for the United States Military

Overview of the Proposed Protocol

The sponsor's goal is to determine the mean level of bite protection (and 95% confidence intervals) for etofenprox-treated uniforms (specifically, U.S. Military Fire Resistant Army Combat Uniforms). Two materials ("coats" (referring to shirts and blouses) and "trousers" – or pants) will be studied in an untreated condition and in three conditions post-treatment with 1% repellent: fabric by weight: before any washings (0x), after 20 washings in hot water (20x), and after 50 washings (50x). Each study subject will be exposed to all four conditions and therefore serve as his/her own control. Each participant will put on a "sleeve" made from one of the two study materials (coat or trousers) in one of the four conditions and place his/her arm in a cage with one of two species of laboratory-raised mosquitoes (*Anopheles* or *Aedes*) for 15

minutes/hour up to 8 hours. The percent bite protection for each 15-minute test will be determined by counting and comparing the number of blood-fed female mosquitoes to the total number or mosquitoes placed in the cage for that test.

Eight people will be recruited into this study, based on calculations showing that little statistical power is gained with a larger number of study subjects; two alternates will be identified. Each participant will be tested 8 times; *i.e.,* four sleeve conditions for each of the two mosquito species. Thus, there will be 16 replicates for each fabric condition group.

Science

Charge to the Board

- Is the protocol "Laboratory Evaluation of Bite Protection From Repellent Impregnated Clothing for the United States Military" likely to generate scientifically reliable data, useful for estimating the level of mosquito bite protection provided by two different textiles treated with etofenprox?

Board Response to the Charge

HSRB Recommendation

- The Board concurred that the proposed protocol will likely generate scientifically reliable data for estimation of bite protection efficacy of impregnated clothing, if improvements in the overall study design enumerated by EPA (Sweeney & Sherman, 2014) and the Board are adequately considered.

HSRB Detailed Recommendations and Rationale

EPA's science review resulted in multiple comments. The Board reiterated several of EPA's recommendations:

- The HSRB agrees that the statistical analysis must be finalized prior to initiation of the study.

- The Board agrees that at least 20 qualified subjects should be identified and that participants be selected at random from that larger group.

- The HSRB is concerned that two alternate participants is an insufficient number due to potential for dropout.

- The Board agrees that the study should not be conducted until a product-specific fabric irritancy study is completed.

The HSRB made the following additional comments:

1. Statistical Design. The proposed protocol is generally well designed from a statistical standpoint. Because the desired scope of inference is beyond the subjects in this study, each subject should be treated as a random effect (not as a fixed effect).

Maintaining the sample size of 8 is a concern to the Board. This number does not allow for the possibility of dropouts; the HSRB recommended that additional participants be recruited so that a pool of alternates is available to ensure that the desired number of 8 completed tests is achieved. Questions were raised about how dropout data would be handled; *e.g.*, would it be analyzed or eliminated?

Furthermore, if one arm of each participant is used as a control, then double the sample size would be needed. To reduce the burden of testing on each participant, another option would be to have 16 participants on whom the tests for only one species are conducted.

Additionally, the number of participants by gender could be restricted, rather than left to chance, in the enrollment process.

If the treatment could be randomized instead of ordered by dose, the study design would be stronger. The Board asked the Agency to reconsider how the treatments will be assigned to participants.

2. Fabric sleeves. The Board believes that provision of a single sleeve size is inappropriate given the possible relationship between snugness of fit and bite protection. A range of sleeve sizes should be available corresponding to at least a portion of the uniform sizes available to soldiers; one-to-one correspondence is not required. However, each subject should be provided sleeves corresponding to their normal garment size. It is desirable to avoid rejecting either large subjects who cannot fit their arms into the "one sleeve size," or small subjects for whom the sleeves will be too loose. The Board heard that most soldiers do not wear their clothing tight; therefore, the HSRB recommended that the standard test conditions be as representative as possible of use conditions in the field. Characterization of the tightness of the sleeve should be recorded to enable comparing test outcomes and thereby gain insights for future protocols.

3. Dermal toxicity. An MOE of 235 was calculated based on a reported 50% Lethal Dose (LD_{50}) of > 2,100 mg/kg/day and an exposure of 9 mg/kg (based on 100% absorption of 635 mg of active ingredient (AI) from six sleeves).[28] This is declared adequate on the grounds that EPA's level of concern is an MOE of 100. Further attention is required to the following issues:

- The protocol from which the LD_{50} was estimated was not provided to the HSRB. If the experiments were conducted under flux limited conditions, the LD_{50} may be artificially high.

[28] The Board noted that 695 mg was indicated in the written materials, but 635 mg was presented during the Board meeting.

- 100% absorption of etofenprox is deemed conservative based on a reported bioavailability of 7%. The protocol from which the availability was estimated was not provided. It is unclear whether the 7% figure includes the agent in the treated skin at the end of the experiment. In addition, fractional absorption is dependent upon loading conditions. The Board recommended examining experimental conditions to determine whether the reported availability reflects flux limited conditions.

- Target MOE's of 100 typically represent 100x a NOAEL, not an LD_{50}. An explanation of this deviation needs to be provided.

4. Bite pressure. The Board noted that "bite pressure" is not clearly defined in this proposed protocol. The HSRB recommended that the term be clarified before the study begins.

5. Carryover. The proposed protocol assumes that each individual will conduct 8 two-arm trials on a single day. These studies would be conducted sequentially using each of two mosquito species. Each within-species protocol would be ordered as follows: untreated sleeves, 50x washed sleeves, 20x washed sleeves, 0x washed sleeves. This sequence minimizes, to the extent possible, carryover effects in within-species testing. However, the 0x sleeves from the first mosquito species will precede the untreated sleeve trials for the second species. Arms are to be washed in between, but the efficacy of washing is unknown. A more conservative strategy would be separation of species trials by sufficient time (days) to allow excretion of absorbed etofenprox.

6. *Additional comments*. The HSRB raised concerns about the possibility of treatment failure. One way to address this concern would be to test repellency effectiveness on one or two participants before the proposed study begins.

The scientific justification for conducting human research was articulated during the Board meeting but is not clearly documented. The Board recommended that the rationale for doing this research on humans be fully built and explicitly stated in the proposal.

Ethics

Charge to the Board

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

Board Response to the Charge

<u>HSRB Recommendation</u>

- The Board concluded that the protocol submitted for review, if modified in accordance with EPA (Sweeney & Sherman, 2014) and HSRB recommendations, is likely to meet the applicable requirements of 40 CFR 26, subparts K and L.

HSRB Detailed Recommendations and Rationale

The submitted documents assert that the study will be conducted in accordance with the ethical and regulatory standards of 40 CFR 26, Subparts K and L, as well as the requirements the US EPA's GLP Standards for FIFRA described at 40 CFR 160 (Bernier, 2014).

The protocol was reviewed and approved by Western IRB (WIRB) of Puyallup, WA, an independent human subjects review committee, prior to submission. WIRB is fully accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP). WIRB is listed as an active IRB on the OHRP website (Reg. # IORG0000432). Minutes of WIRB's meetings and a copy of WIRB's policies and procedures were provided to the Agency. These documents indicate that WIRB reviewed this protocol pursuant to the standards of the Common Rule (45 CFR Part 46, Subpart A).

1. Except as noted below, the Board concurred with the conclusions and factual observations of the ethical strengths and weaknesses of the study, as detailed in the EPA's Ethics Review (Sweeney & Sherman, 2014, pp. 2-5). The proposed study is likely to meet the applicable ethical requirements for research involving human subjects, in accordance with the following criteria:

a. Risks to participants are commensurate with anticipated benefits to participants or society. The HSRB identified four risks in the study protocol: 1) risk of exposure to biting arthropods, which includes discomfort from bites, subsequent itching, secondary infection from scratching, and allergic reaction; 2) risk from exposure to disease vectors; 3) risks from exposure to the test material, including allergic reaction to chemical repellents and latex from the outer glove; and 4) psychological stress from pregnancy testing and/or breach of confidentiality for pregnancy test results.

   These risks are minimized appropriately, are characterized as of low probability, and are justified by the potential societal benefits associated with data on repellent treatment for military clothing. There are no direct benefits to individual subjects.

   - Individuals who are hypersensitive to mosquito bites and those who are phobic about mosquitoes will be excluded from the study.

   - Participants will be informed that itching is likely to be the most significant discomfort they will experience. An over-the-counter topical steroid cream will be available for use immediately upon completion of the tests. Participants who become uncomfortable from itching may stop the test. A nurse familiar with the study protocol will be on call to assist if needed.

   - Mosquitoes used in the study will be exclusively from laboratory-bred colonies, and will be screened for disease vectors before use, making the risk of disease transmission negligible.

   - Only compounds with no clear association with allergic reactions will be tested. People who are known to be allergic to the test compound or to latex will be excluded from the

study. Only the forearm will be exposed. The potential risks to participants from test materials are minimized by exclusion of individuals who are sensitive to the test materials.

- Appropriate stopping measures are in place in the event of an injury or other adverse outcome.

- Minors and pregnant or lactating women are excluded from taking part. Pregnancy is either confirmed by over-the-counter pregnancy testing on the day of study or by opt-out. Only volunteers whose test results show them to be non-pregnant will be allowed to participate. Potential stigma resulting from exclusion due to pregnancy is appropriately minimized. Testing is done in private and with the option of discrete withdrawal. Information regarding pregnancy test results will be kept confidential.

b. Voluntary and informed consent of all participants

- The Board respectfully disagrees with the Agency's conclusion that "no potential subjects are from a vulnerable population" (Sweeney & Sherman, 2014, p. 22). Rather, a better description is that the study is not actively recruiting participants that come from potentially vulnerable populations. There is a possibility that some participants in this study might be vulnerable, susceptible to coercion and undue influence. The study protocol, however, includes several mechanisms designed to minimize coercive recruitment and enrollment.

- Research participants will be recruited through printed advertisements in English in the local Gainesville, FL, newspaper and posted on bulletin boards at the University of Florida. The ability to speak and read English is a requirement of participation, resulting in a generally literate subject population, typically less subject to coercion.

- The informed consent materials, if modified as recommended by the HSRB below, will adequately inform the subjects of the risks, discomforts and benefits from participation, and of their right to withdraw from the study at any time.

- Monetary compensation is not so high as to unduly influence participants.

c. Equitable selection of study participants

- The protocol is designed to recruit participants from an appropriately diverse population likely to represent the diversity of members of the military who are the intended users of the treated clothing, with a similar over-representation of younger individuals.

2. The Board recommended that the study protocol and informed consent document be modified to address the concerns noted in the EPA's Ethics Review (Sweeney & Sherman, 2014). In addition, the Board raised the following concerns:

a. Although a question about allergy/sensitivity to latex is listed on the enrollment questionnaire, latex allergy/sensitivity does not appear as an exclusion criterion in the recruitment interview script or consent document. Latex allergy/sensitivity should be included in all statements of exclusion criteria. Alternatively, the protocol could be modified to use nitrile gloves instead of latex.

b. The protocol currently calls for test sleeves to be made in a single size, despite the likely variation in arm size among participants and 34 different uniform sizes available to military personnel. The single sleeve size may both skew the results of the testing across participants of various arm sizes and it may also cause embarrassment to participants who attempt to put on sleeves that do not fit easily. The Board recommended that researchers include a question about shirt sleeve size in the recruitment interview and have test sleeves available in different sizes.

c. Currently, stopping rules depend on researchers' judgment on key criteria of subjects' attractiveness and sensitivity, and mosquitoes' biting pressure. (Bernier, 2014, p. 46). The Board recommended that the investigators articulate objective measures for stopping criteria.

d. The Board noted that clarification is needed in the consent form about a nurse being on call but not present at the study site.

e. Currently, partial (per sleeve) compensation is provided to participants who leave the study early for any reason. The HSRB recommended that, to prevent coercion or to compensate for dropping out or being excluded by the Principal Investigator (PI), full compensation be provided to all participants.

f. Language in the consent form indicating that laboratory mosquitoes pose no risk of transmitting disease needs to be modified. To address the unlikely possibility that any of the test mosquitoes is found to carry a disease, investigators should articulate a standard method and message for notifying participants of exposure.

g. It is recommended that researchers complete a course in human subjects protections within three years of study initiation and completion. Depending on when the study occurs, some investigators may exceed this recommended time limit.

Background Presentation on the Repellency Awareness Graphic and Possible Implications for the HSRB

Staff of EPA's Office of Pesticide Programs presented background and current information about the Repellency Awareness Graphic; it has been developed in response to public requests for clearer labeling of insect repellent products. Graphics were developed and pretested using focus group methods. The three final graphics show the number of hours which the skin-applied product will repel ticks and/or mosquitoes. Standardization of the graphic is expected to increase public understanding of product capabilities so they can more readily identify which products will meet their needs. The Agency's draft guidance for this graphic is out for public comment until November 13, 2014.

Board members asked several questions of clarification and raised some concerns. For example, one concern was how the Agency would use data from multiple studies to determine the number of hours displayed. Staff recognized that some companies will not have all of the data needed to complete the graphic for their product; they expect registrants to request a standardized protocol to obtain the necessary data. EPA staff would present the proposed protocol to the HSRB for review before studies would be approved. A question was asked about whether a standardized protocol would ensure best scientific practices or not.

Another concern was how a median Complete Protection Time (CPT) would be determined across mosquito and tick species. Furthermore, it was suggested that the lowest, rather than the median, CPT would be more conservative.

Report from the HSRB Work Group on the Return of Individual Research Results

A consultant to the Board provided information about the origin of the Work Group and summarized the group's report to the Board. He noted that in the 2009-2010 period the HSRB had received a protocol in which the sponsor included a draft letter to return study results to participants. On several occasions the HSRB had discussed return of research results, but determined that the topic merited in-depth discussion by a smaller group of Board members and representatives of study participants and their medical providers. A Work Group was formed to deliberate this issue; the workshop was held at EPA in January 2013. The Work Group membership, its process and report with an appendix are presented together in Appendix A.

As noted in the appended report, return of research results has been addressed for clinical studies and some community-based research but not for the types of laboratory or field studies within the HSRB's purview. The return of results is a timely, unresolved and evolving issue in the ethics profession.

The Work Group identified key ethical principles as the underpinnings of their deliberations: research participant's autonomy and right to know, and researchers' responsibilities to ensure trust and respect. The group discussed the potential impacts of results on participants and sponsors, as well as the HSRB and the Agency. The Work Group made three recommendations for the HSRB's consideration.

1. For many intentional exposure studies, individual results are unlikely to be clinically relevant. Despite this, study sponsors or investigators have an obligation to offer results to participants.
2. There is an absolute moral obligation to return aggregate results directly to all participants (*e.g.*, via a letter written in lay language), unless the participant declines of [sic] notification.
3. There is a presumptive moral obligation to return individual results in a way that is comprehensible, contextualized, relevant and useful if a study participant asks for them.

The Board asked clarifying questions and discussed the report. The HSRB agreed that the clinical setting is not a suitable framework for considering return of individual results to participants in intentional exposure studies. The question was raised as to whether actionable

exposure levels occur and whether the levels are always known to the participants. One Board member stated that the ethical principle of social justice points to always offering results.

Although the Board showed considerable interest in the report, there was insufficient time during this meeting to identify recommendations for the Agency. Furthermore, the recent release of the President's Bioethics Commission on Incidental Findings may inform the HSRB's deliberations and decisions; this report was not available for this meeting. The Board agreed to discuss the issue of returning individual results to study participants at a subsequent meeting.

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APPENDIX A

Work Group on Return of Individual Research Results
Human Studies Review Board
US EPA

Meeting Report and Recommendations

Charge to Work Group

To provide advice, information and recommendations to the US Environmental Protection Agency's (EPA's) Human Studies Review Board (HSRB) on the issue of returning individual research results.

Background

It is generally accepted that, in a clinical context, physicians and other health care providers have an obligation to inform patients about the results of individual diagnostic tests (see, e.g., American College of Physicians [2012]). These tests are being performed solely for the benefit of the patient and the results will have an effect on individualized treatment. As clinicians have an obligation to provide the best care possible and an obligation to respect the right of patients to make voluntary and informed decisions about treatment, disclosure of individual test results is an ethical imperative.

By contrast, there is little consensus as to whether or not investigators have an ethical obligation to inform study participants about the results of tests performed on them as part of a research protocol (see, e.g., testimony from the August 19-20 meeting of the US President's Council for the Study of Bioethical Issues [PCSBI]. PCSBI [2013]). Often, the primary goal of research is not to benefit the individual participant directly but rather to benefit society in general. Research tests and procedures are often done primarily for hypothesis testing or generation, rather than to diagnose disease or to inform physicians and patients about appropriate treatments. These tests also may not be clinically validated or may not be performed in certified laboratories following rigorous quality control standards; it is often illegal to release individual test results that are not performed under these conditions (Clayton et al. 2013). There is a general ethical presumption that study participants should be informed of aggregate and de-identified research findings. However, there is still considerable disagreement about if and when individual subjects should be told about their own individual results from tests performed on them as part of research.

US Federal regulations are largely silent on this topic (see. e.g., Code of Federal Regulations Title 45: Public Welfare. Department of Health and Human Services. Part 46: Protection Of Human Subjects). The only thing that current regulations require is that study participants be told explicitly as part of the consent process about whether or not they will be given research results. They should also be told of new results that may change their decision to participate in the study. There is no statutory requirement to provide individual research results.

Most discussions of researchers' ethical duties to return individual results have focused on reporting incidental findings, usually in the context of genetic or neurological research (Green et al. 2013a; Sandeman et al. 2013; Wolf 2013). If researchers performing genome-wide association studies (GWAS) of genetic factors potentially associated with diabetes, for example, are they obligated to notify a participant if they discover that the subject carries the genetic markers associated with Huntington's disease or hereditary breast cancer? Would a neurobiologist conducting studies of spatial memory using functional magnetic resonance imaging (fMRI) be required to tell a research participant that they have abnormal neural connectivity in the brain?

These debates are usually framed in terms of a duty to warn, with researchers having an obligation to inform research participants of findings that have serious clinical implications (Wolf 2013). The ethical principle of beneficence – the obligation of investigators to maximize potential benefits and minimize potential risks of study participation – would seem to suggest that research participants be told those test results that could directly benefit their health. This would be true in cases where the test results are clear, the clinical implications unequivocal, and treatment or care available.

From this perspective, when there is uncertainty about the test results or their clinical implications the obligation to inform subjects may or may not exist. Some argue that providing individual research results can provide benefit. Research participants in the study of genetic factors potentially associated with diabetes, for example, might use information about potential risks of developing diabetes or other chronic conditions to make lifestyle choices that might reduce the likelihood of developing disease (see, e.g., Affleck 2009). Others make the case that providing individual research results is itself a benefit because it demonstrates respect for participants, honors the participants' right to know, and has the potential to strengthen trust in the investigators and in the research endeavor (Ravitsky and Wilfond 2006).

Others have argued, however, that informing study participants of uncertain or probabilistic test results might actually lead to physical, psychological or social harm (Moynihan et al. 2012). A person who is told that they are likely to develop Huntington's Disease, a progressive neurodegenerative condition for which there is currently no cure, might use this information in a positive way – for example, by making decisions about if and when to have children, each of whom could also carry the trait – or they might react to this disclosure in a negative way – for example, by becoming psychologically depressed or even considering suicide (Lewis 2013).

There is still considerable disagreement about the ethical obligation to return individual results, but some areas of consensus have begun to emerge (Green et al. 2013b). For example, there is some consensus that the duty to disclose individual test results of clinical research increases in proportion to the level of certainty that the information provided will positively affect the diagnosis, prognosis and treatment of the individual. In addition, there is some consensus that researchers should carefully consider the possibility that disclosing research results may harm research subjects. Finally, there is general agreement that researchers should inform research participants about if, when and how individual findings will be communicated.

These considerations are particularly challenging for investigators conducting studies related to the charge of the HSRB, namely intentional exposure studies of compounds under the regulatory authority of the EPA.

Historically, such studies have been conducted using exposure chambers under controlled laboratory conditions, with participants informed of exposure levels as part of the informed consent process (see, e.g., Muttray et al. 2013 and Bartoli et al. 2013 for recent examples of these sorts of studies). A number of recent intentional exposure studies submitted to the HSRB for review, however, have involved observational analysis and measurement of dermal and inhalation exposure to EPA regulated compounds under real-world conditions. Investigators conducting these studies have proposed providing study participants with individual exposure results, despite uncertain benefits. These studies, for instance, are designed only to measure exposure levels, not health effects. In addition, most of the intentional exposure studies that have been reviewed by the HSRB to date were designed to measure levels of exposure that are well below established thresholds for acute toxicity. Finally, these tests are used to measure exposure and are not clinically validated; they are not clinical tests at all.

The prevailing assumption in the current debate about individual research results is that they should be returned only if they are clinically relevant or otherwise actionable. Providing individual results is unlikely to provide any clear or direct health benefit to intentional exposure study participants. Any benefit would likely be informational only, and there is little empirical evidence published to date that suggests that this information would help people reduce their future exposures. However, a growing body of literature from public health ethicists and environmental advocates, among others, suggests that this presumption -- that participants must benefit clinically if individual results are to be returned -- is too narrow and fails to consider issues of subject autonomy and participatory and reciprocal justice (Morello-Frosch et al. 2009; Parkin 2004).

Because of these concerns, study sponsors and the Agency have sought the input of the HSRB on if and when to release individual exposure data to observational study participants, leading to the formation of the Work Group on Return of Individual Research Results.

Work Group Process

The Work Group on Return of Individual Research Results is made up experts in research ethics, community-based participatory research, health risk assessment, toxicology and biostatistics.

The Work Group, which includes both current and former members of the HSRB as well as independent consultants, met for a one-day face-to-face meeting on January 16, 2013 to consider the following questions:

1. In research studies that involve intentional exposure of participants to EPA regulated compounds, do researchers have a moral obligation to offer individual research results to participants? Why or why not?
2. What are the circumstances under which there is a moral obligation to return individual research results to participants of intentional exposure studies?

3. What is ethical basis for any obligation to provide individual research results to participants of intentional exposure studies? Is there an ethical basis for not offering individual research results?

Group discussion of whether or not it is ethically obligatory to return individual research results to study participants was structured around three scenarios adapted from real-world intentional exposure studies submitted to the HSRB for review. These scenarios are summarized below:

Scenario 1: Measurement of dermal and inhalation exposure to a liquid antimicrobial pesticide product applied using a bucket and mop.

Participants include English- and Spanish-speaking janitorial professionals of both genders, recruited using flyers soliciting interest posted at janitorial service companies. Subjects will apply a commercially available (low toxicity) cleaning product to floors using a string mop and bucket for predetermined amounts of time. Activities include mopping and emptying of the mop bucket, but not mixing of the antimicrobial solution. Exposure will be assessed using a whole body dosimeter, hand wash and face wipes, and OHSA Versatile Sampler (OVS) tube sample collection.

Scenario 2: Measurement of dermal and inhalation exposure to a liquid pesticide applied using a backpack or handgun sprayer in utility rights-of way.

Participants include English-speaking utility workers of both genders, recruited using brochures posted in utility company workspaces. Subjects will be engaged in their regular duties as utility workers, applying a commercially available EPA-registered pesticide using a vehicle-mounted handgun or backpack applicator. Exposure will be assessed using a whole body dosimeter, hand wash and face wipes, and OHSA Versatile Sampler (OVS) tube sample collection.

Scenario 3: Dosimetry and effectiveness testing of personal insect repellents under field conditions.

Participants include English-speaking subjects recruited from a database of potential volunteers using a random dialing approach. The database is owned by a contract research organization that recruits potential subjects via advertisements in local newspapers. The study consists of two independent analyses: 1) a laboratory-based dosimetry study to determine the amount of repellent that typical users would apply; and 2) a field-based study of repellent effectiveness. Two formulations of a conditionally registered repellent would be used: a lotion and a spray. Exposure during the laboratory phase would be measured by passive dosimetry using self-adhesive gauze (spray) or by direct measurement (lotion). During the field tests the amount of repellent applied would be standardized, and repellent effectiveness determined by exposure to mosquitoes in a natural environment.

Work group members were asked to address the three charge questions listed above for each scenario, with the group Chair facilitating the discussion in an attempt to reach consensus. If consensus could not be reached on a recommendation and rationale for the HSRB, the majority opinion would be presented to the Board with minority views represented in the associated commentary. For each of the recommendations listed below, consensus was achieved. During subsequent decision of this meeting report, however, one Working Group member raised concerns about Recommendation 3. These concerns are detailed in the attached memo (Appendix 1).

Recommendations

1. For many intentional exposure studies, individual results are unlikely to be clinically relevant. Despite this, study sponsors or investigators have an obligation to offer results to participants.

2. There is an absolute moral obligation to return aggregate results directly to all participants (e.g. via a letter written in lay language), unless the participant declines of notification.

3. There is a presumptive moral obligation to return individual results in a way that is comprehensible, contextualized, relevant and useful if a study participant asks for them.

Rationale

Different ethical frameworks can and have been used to explore the issue of returning research results to participants. However, most of the discussions have been framed around the three principles of *respect for persons*, *beneficence* and *justice*. These three principles are widely recognized and provide a moral foundation for current US regulations and guidance for the ethical conduct of research involving human participants. Support for the Work Group's conclusions can be found in each of these principles.

For example, the principle of *respect for persons* requires that investigators treat research participants as autonomous moral agents capable of making decisions for themselves. In practice, this requires that research participants be allowed to make a voluntary and fully informed choice about whether or not to participate in a study. Included in this is the obligation for investigators to provide to potential volunteers, in a comprehensible and culturally appropriate manner, all information about the study that the participants deem relevant. This includes information about the risks and benefits of participation, and how the results of research will be disseminated to the participant and the community. However, the informed consent process does not end once the participant has agreed to enroll in the study. Rather, it is an ongoing conversation, with participants free to leave the study at any time and for any reason. Moreover, investigators are obligated to communicate to participants, "significant new findings … which may relate to the subject's willingness to continue participation" (45 CFR 46.116(b)(5)).

The Work Group concluded that respect for persons also extends to informing research participants of results even after the study has ended, as these results may have significant implications for the participants. For example, such data may inform participants of potential workplace risks or provide them with information about reducing workplace exposure to potentially hazardous chemicals like pesticides. It is the individual participant's right to decide if they want to know the results or not, as well as to decide what they will do with this information. Thus, the study sponsors and investigators are morally obligated to offer research results to study participants. It is important to note, however, that this is different from mandatory provision or disclosure of results to participants. As autonomous agents, research subjects also have the right to decline to be given research results.

Similarly, the principle of *beneficence* requires that investigators maximize the potential benefits and minimize the predictable risks of study participation. In the case of intentional exposure studies, the likely benefits to individual research participants are primarily informational. Janitorial or utility workers who routinely handle potentially hazardous chemicals like pesticides may benefit from learning about chemical exposures that are part of their jobs. As exposure is part of these workers' jobs, study participants as a class will likely benefit from disclosure of results.

Some study sponsors and investigators worry that disclosure of research results may pose some risk to participants. Providing research results, for example, might cause psychological distress in those with higher than average exposures or prompt those with lower than average exposures to relax their workplace safety habits in ways that may put them at increased risk of harm. But these risks are individual and unpredictable. Therefore, the moral obligation to minimize risks of study participation does not preclude returning of research results. Potential risks to individual participants do not justify denying likely benefits to all participants. Rather, it requires that investigators return research results in a way that is comprehensible, relevant, contextualized and usable to those who request this information.

Finally, the principle of *justice* requires that research subject selection be equitable and non-exploitative. Individuals and groups that participate in research should benefit, and the study should be responsive to their concerns and needs. There are different concepts of justice: distributive, participatory, rectificatory, and reciprocal. When applied to the research context, the fourth of these – reciprocal justice – suggests that individuals who voluntarily take on the risks of research deserve proportionally more benefit. People who contribute to the research effort deserve something in return, be it access to new treatments, provision of ancillary care or, in the case of non-clinical research like intentional exposure studies, the offer of research results. In the long term, providing these results also demonstrates openness and transparency, building trust between the investigators, the study participants and the larger community.

The Work Group thus found that ethical principles of *respect for persons*, *beneficence* and *justice* place a moral obligation on study sponsors and investigators to offer research results to all study participants. At a minimum, researchers must provide aggregate results to all participants except those who decline notification. Similar moral arguments could be made with respect to returning individualized results to participants, but in its discussions of the three exposure

scenarios the Work Group concluded that there was only a presumptive rather than an absolute obligation to return these results if the subject asks for them.

Depending on the context and goals of the study, sponsors and investigators may be justified in some circumstances in withholding individual results. In particular, the *relevance* and *usability* of individualized results is important in determining if and when these data should be reported. For example, in two of the scenarios discussed – Scenario 1: Measurement of dermal and inhalation exposure to a liquid antimicrobial pesticide product applied using a bucket and mop and Scenario 2: Measurement of dermal and inhalation exposure to a liquid pesticide applied using a backpack or handgun sprayer in utility rights-of way – research participants are professional janitorial and utility workers who use potentially hazardous chemicals routinely. Exposure to these chemicals is not voluntary but is a routine part of their jobs. Thus, there is a strong obligation to return individualized results to participants in these studies as they may be directly relevant to the risks they experience in the workplace and may be of considerable utility (e.g. it may improve safe chemical handling and reduce future exposures, particularly for those with higher than average results). However, these results must be presented in a way that is comprehensible and contextualized, and which minimizes potential psychological and social risks.

By contrast, in Scenario 3 (Dosimetry and effectiveness testing of personal insect repellents under field conditions), the relevance and usability of individualized results was questionable. Participants in this study were healthy volunteers who may or may not be exposed to the test chemical in the future. Even if they are – by using a commercially available formulation of the insect repellent being tested, for example – the individual exposure data obtained during the dosimetry experiments may not be directly comparable to use of a consumer product. Providing individualized results in this case might be morally praiseworthy but not ethically obligatory.

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Appendix 1: Memo of Concern

From: Sammy Almashat, MD, MPH
Physician and Staff Researcher, Public Citizen
Member, Work Group on the Return of Individual Research Results

To: EPA Human Studies Review Board

Re: Disagreement with Work Group recommendations to the Human Studies Review Board

I am writing today to express my partial disagreement with the Work Group on the Return of Individual Research Results recommendations on the moral obligations of investigators to offer individual research results to human subjects in intentional exposure studies.

I wholeheartedly support the general intent of the Work Group's recommendations and their rationale for supporting greater transparency in the disclosure of research results.

I also strongly endorse the recommendation that places an absolute moral obligation on investigators to return aggregate research results to subjects, regardless of the relevance or usability of the data, unless the subject declines the offer.

However, I disagree with the recommendation that there is only a presumptive (rather than absolute) obligation to return individual research results, "only if they can and will be presented in a way that is comprehensible, contextualized, relevant and useful." (Working Group on the Return of Individual Research Results, 2013). Rather, the return of individual research results (especially if requested by the subject on an "opt-in" basis) constitutes an absolute moral obligation as a subject's right to know overrides questions of relevance and practical utility.

My objections are for the following reasons:

1. **The moral obligation to return, or not return individual research results should not rely on the investigator's or study sponsor's determination of the relevance or utility of the information.**

   I am concerned that determinations of the relevance and utility of individual research results will be made solely by the investigator or study sponsors. The relevance of a particular set of data is, in part, a subjective determination made by each individual subject (e.g. the simple desire to satisfy one's curiosity is relevant to the subject in a way that cannot be measured objectively). For exposure data in particular, it is often challenging to identify significant clinical consequences from disclosure (or non-disclosure) of the information. It will also be challenging for study investigators to determine the objective relevance (or evaluate the solicited subjective relevance) of research results for *each individual subject*, particularly in large studies involving

heterogeneous groups and highly variable exposure results. For these reasons only the respective subject can determine the relevance and utility of individual research results.

Another concern that arises from the exclusive reliance on study investigators' determination of relevance and utility is a potential tendency among investigators and sponsors, however subtle and unconscious, against providing more information than is absolutely required. Returning individual research results represents a financial and time commitment on the part of the study sponsor that is considerably greater than the return of a single, identical set of aggregate results. The Work Group's recommendation (with which I agree) to make the individual results "comprehensible, contextualized, relevant and useful" adds to the scale of the commitment. Therefore, some sponsors may, in the face of the uncertainty inherent to the abstract notions of "relevance" and "utility," but not necessarily out of any malintent, too often err against returning individual research results.

2. **The potential for unintended harm, not the relevance or utility of individual results, should serve as the sole basis for the determination of the moral obligation to return individual research results in intentional exposure studies.**

   The sole consideration relevant to the question of whether or not there is a moral obligation to returning individual results should be the potential for unintended harm to the subject, in the form of psychological, social, or economic difficulty incurred as a result of the disclosure of such information.

   Here, I agree with the Work Group's assertion that, "the moral obligation to minimize risks of study participation does not preclude returning of research results" (Working Group on the Return of Individual Research Results, 2013). While the return of aggregate results raises similar concerns of unintended harm, the Working Group did not consider this to be sufficient to exempt investigators from the absolute requirement to return such results in all cases, unless subjects actively decline receipt of the information. In fact, returning aggregate results in the absence of individual results could make the information less relevant to each individual subject. Such a situation of increased uncertainty as to how the aggregate results apply to the individual subject could heighten anxiety or it could mitigate it.

   It is also true that the return of individual research results in a way that is not readily comprehensible or interpretable may cause more unintended harm than the return of aggregate results alone. However, here the critical point to consider is that the potential for unintended harm to research subjects as a result of the disclosure of individual research results increases (and decreases) in direct proportion to the relevance or utility of the information to the subject. For example, in scenarios #1 and #2 discussed by the Working Group (Working Group on the Return of Individual Research Results, 2013), potential harms were anticipated only because the exposures studied were relevant to the subjects in some way (e.g. the same potentially dangerous exposures were also present at their worksites). By contrast, in scenario #3, no unintended harms were identified presumably because the exposure was not deemed relevant to subjects' everyday lives. In other words, it is precisely the studies in which

individual results are *least relevant* to subjects' lives that are *least likely* to cause unintended harm to the subject.

In cases in which the potential for harm resulting from disclosure of individual research results is particularly high, investigators should be obligated to inform subjects of this possibility. In light of the Work Group's recommendation for the obligatory return of aggregate results in all circumstances, it is hoped that subjects would be warned of the potential for unintended harm caused by the return of aggregate results. With minor modifications, a similar warning should accompany the return of individual results. Empowering subjects to make informed decisions for themselves enhances autonomy and fosters trust in the research process.

3. "Opt-out" vs. "opt-in" for aggregate and individual research results

While the Work Group's charge was limited to the determination of *whether* a moral obligation should exist to return research results, a consideration of *how* research results should be returned in light of the discrepant moral obligations for aggregate and individual research results is warranted.

I agree with the Work Group that the return of aggregate results should always occur on an "opt-out" basis so as to minimize the number of subjects failing to receive the information for a lack of awareness of their right to do so. I disagree, however, with the proposal for an opt-in system for individual research results. The presumption of lower relevance and utility and a higher likelihood of harm associated with the return of individual versus aggregate results may explain why different standards (i.e., absolute versus presumptive moral obligations) were applied.

As outlined above, I disagree with these assumptions. I believe that an opt-out system should be applied in both cases. Should an opt-in system be adopted for the return of individual research results, however, investigators should be required to disclose this option to subjects during the informed consent process and after study completion.

Work Group on Return of Individual Research Results

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