UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

OFFICE OF CHEMICAL SAFETY AND
POLLUTION PREVENTION

March 15, 2018

MEMORANDUM

SUBJECT: Ethics Review of Completed AEATF II Study AEA08 – Handwash Removal Efficiency (AEATF II Project ID AEA08; MRID 50521601)

FROM: Michelle Arling, Human Research Ethics Review Officer
Office of Pesticide Programs (OPP)

TO: Laura Parsons, Acting Branch Chief
Risk Assessment and Science Support Branch (RASSB)
OPP/Antimicrobials Division (7510P)

REF: Boatwright, Megan. (2017) Determination of Removal Efficiency of 1,2-Benzisothiazol-3(2H)-one (BIT) from Hand Surfaces Using an Isopropyl Alcohol/Water Wipe and Wash Procedure. Study Number AEA08, 1286 p. June 23, 2017 (MRID 50521601)

I have reviewed the available information concerning the ethical conduct of the research reported by the Antimicrobial Exposure Assessment Task Force II (AEATF) in the referenced documents. The documents describe the implementation and results of a study whose objective was to determine the removal efficiency of BIT in latex paint from human hands. The results of this study would be used to analyze the results of study AEA09, a study conducted to determine the potential dermal and inhalation exposure for consumers (i.e., non-professional painters) using a brush and/or roller to apply latex paint containing an antimicrobial pesticide (BIT).

In its conduct, study AEA08 met applicable ethical standards for the protection of human subjects of research, and requirements for documentation of ethical conduct of the research were satisfied. Therefore, if study AEA08 is determined to be scientifically acceptable, I find no barrier in regulation to EPA's reliance on the results in actions under FIFRA or §408 of FFDCA.

In addition, under 40 CFR 26.1604, EPA is required to seek input from the Human Studies Review Board (HSRB) for intentional exposure human studies covered by EPA's human studies rule that are initiated after April 7, 2006. EPA will share study AEA08, the associated support documents, and EPA's science and ethics reviews of the study with the HSRB for their review. This memorandum and its attachments constitute EPA's ethics review.

Summary Characteristics of the Research

Study AEA08 developed data to determine the removal efficiency of BIT in latex paint from human hands. To accomplish this, latex paint containing one of two concentrations of BIT (~154 ppm or ~547 ppm) was applied to subjects' palms and allowed to dry for 45 minutes. After the specified time elapsed, wipes and 50/50 solution of isopropyl alcohol and water were used to wash the hands, and the liquid and wipes used in the handwashing process were collected for analysis.

The study was conducted on April 7 and 9, 2015 at Golden Pacific Laboratories (GPL) in California. Of a total recruitment pool of 40 respondents, 28 subjects were selected randomly – 20 test subjects, and 8 alternates. The test was conducted in 4 events, in each of which 5 subjects and 2 alternates were scheduled to participate. A total of 20 subjects completed the handwashing study (i.e., a total of 20 monitoring events/MEs).

When the subject arrived at the test facility for the assigned ME, the subject was asked if he or she had any questions and was reminded that he or she could withdraw at any point before or during the ME. A nurse checked the subject's hands for skin conditions that would disqualify him or her from participation. Females took a urine pregnancy test in a private location, and a female study staff member confirmed the results. Each subject washed his or her hands and face with soap and water, then at the table where the testing would occur. Once the subject was seated at the table, 100 ul of BIT-fortified paint was applied over both palms using a glass rod. Forty-five minutes after the paint was applied to subjects' hands, researchers helped the subjects to an area where their hands were washed using a wipe and wash procedure. After this was completed, subjects washed their hands, the skin on their hands was checked by a nurse for signs of irritation, and the subjects compensated for their participation and free to leave.

1. Value of Research to Society

This study measured the removal efficiency of the antimicrobial active ingredient BIT in latex paint from human hands. The data produced allowed the interpretation of results from a subsequent study measuring exposure of consumer painters who apply latex paint containing BIT (AEA09). Because many professional and nonprofessional painters use latex paint containing antimicrobial products, the research question is important; it cannot be answered with confidence without new monitoring data meeting contemporary standards of quality and reliability.

2. Subject Selection

a. Recruitment

Recruitment was conducted according to the approved protocol. The protocol called for advertising in 3 papers the Fresno Bee, Vida en el Valle (Fresno edition; Spanish language), and California Advocate. Recruitment ads approved and translated by the IRB were provided to all 3 papers on March 4, 2015. The Fresno Bee and Vida en el Valle published the advertisements, but the California Advocate did not. The study team reported that in response to the ad provided to the California Advocate, "California Advocate responded with a quote, size of space, and confirmation there was space available in the publications of March 9th and 16th, but never provided a proof. Although GPL attempted to contact the newspaper multiple times, the California Advocate staff did not follow up and the advertisement was not published in this newspaper." (p. 169 of 1286) This failure to advertise in all three publications was reported to the IRB as a deviation, but did not affect overall recruitment for the study.

Those who called to express an interest in participating were given general information about the study and asked basic questions about their eligibility. Those who were potentially eligible and still interested were invited to the testing facility for an in-person consent meeting.

b. Demographics

Following the recruitment process described in Section 2.a. above, 40 subjects were enrolled in the study. Each was assigned a consecutive number in the order of their enrollment. Once enrollment was closed, the numbers were randomized; the first 28 numbers identified the initial group of subjects (20 subjects, 8 alternates). The remaining enrolled subjects were held in reserve and invited to participate in the event additional test or alternate subjects were needed. A total of 5 additional subjects beyond the initial pool of test and alternate subjects were invited to participate. The protocol was amended to revise the randomization process and to divide each test day into a morning and afternoon session and to include 5 test subjects in each of 4 sessions.

A total of 20 subjects completed the handwashing study – these subjects ranged in age from 18-67; 12 were male, and 8 were female. Three of the subjects who completed MEs were originally enrolled as alternates and three were originally enrolled as extras. Test subjects were replaced for several reasons: test subjects did not show up on the scheduled day of monitoring, were unable to confirm their ability to participate after being scheduled for a test day, arrived late on the day of testing, and withdrew from the study prior to the test day.

The study report includes additional information about all subjects enrolled in the study on pages 41-44.

c. Inclusion/Exclusion Criteria

Subjects were screened against the inclusion and exclusion criteria in the protocol (pp.75-6 of 1286). Subjects were at least 18 years old; considered themselves in good health; did not have skin conditions on the hands; spoke English or Spanish; and did not have allergies or sensitivities to latex paints, the test substance (BIT), soaps, alcohol, or other chemical products. Age was verified with a government-issued photo identification. Pregnant and lactating females were excluded from participation. On the day of their MEs, females were required to take a pregnancy test as described in the protocol, and negative results were verified by a female member of the study team prior to exposure of female subjects. Female candidates were asked to confirm that they were not lactating during the screening process. Anyone with respiratory or cardiovascular health issues, diabetes, or immunosuppression was excluded. Subjects were not employees or spouses of employees of the study sponsor, entity conducting the study, paint manufacturer, or American Chemistry Council.

Subjects also completed a “Qualification Worksheet” (p. 120 of 1286), which included questions about the inclusion and exclusion criteria and which was reviewed by the interviewer. This form includes an area for the interviewer to indicate that they verified the potential subject’s age during the interview/consent process.

3. Risks and Benefits

The risks of participation in the study included 1) the risk a reaction to the latex paint or BIT, 2) the risk of irritation from use of rubbing alcohol, 3) risk of discomfort, 4) psychological risks, and 5) risk of unintentional release of confidential information/loss of privacy.

Risks to subjects were minimized by enrolling healthy subjects; not enrolling subjects with allergies or sensitivities to the test substance, latex paint, or rubbing alcohol; having medical personnel on-site during monitoring events; alerting subjects to signs and symptoms of a skin reaction; providing chairs and a padded surface on which subjects could rest their arms during the 45 minute waiting period; providing entertainment (television) and offering assistance to subjects if they were uncomfortable during the 45 minute waiting period; providing subjects with a copy of the

product SDS and paint labeling; and checking subjects' skin prior to the ME for signs of skin conditions that could be exacerbated by participation.

The research offered no direct benefits to subjects. The primary benefit of the research is to support interpretation of the data from study AEA09, which is being conducted to generate new data about the dermal and inhalation exposure of individuals who apply latex paints containing antimicrobial pesticides. EPA and other regulatory agencies will use this information to support exposure assessments for a wide variety of products containing antimicrobial pesticides with similar use patterns.

In this study, risks to subjects were minimized. The low residual risk was reasonable in light of the benefits to society from supporting the interpretation of data generated under study AEA09, which will allow EPA to generate more accurate inhalation and dermal exposure assessments for products containing antimicrobial pesticides and applied in a similar manner.

4. Independent Ethics Review

EPA and the HSRB reviewed the protocol for study AEA08 in April 2014. The AEATF submitted the AEA08 protocol to EPA with a conditional approval from Schulman IRB, based on the pending review from the California Department of Pesticide Regulation (CDPR) and incorporation of recommendations from EPA and the HSRB. AEATF also provided to EPA copies of communications with and approval of the protocol by CDPR. This review was required under California's Code of Regulations because the proposed study location was in California.

The protocol and EPA's ethics review[1], dated March 14, 2014, were discussed by the HSRB at its April 8-9, 2014 meeting. With regard to ethics, the HSRB's June 24, 2014 final meeting report concluded that, "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 part 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."[2]

EPA and the HSRB made specific recommendations about the protocol, recruitment materials, and consent forms for AEA08. Attachment 1 contains EPA's summary of the ethics-related recommendations from EPA's review of the protocol and the HSRB's final report, and how AEATF addressed them.

The protocol for AEA08 was reviewed and granted final approval by Schulman Associates IRB on February 9, 2015. Schulman IRB provided certified Spanish translations of all relevant documents related to AEA08 following approval of the final protocol and English versions of recruitment and consent documents.

After the protocol was approved, there were two amendments and three reported deviations. The first protocol amendment was approved by the IRB on March 27, 2015, in advance of the test days. This amendment revises the amount of test substance applied to align with recommendations from EPA and the HSRB, modifies the application procedure, revises the inclusion criterion from

[1] Leighton, Sherman, & Cohen. Science and Ethics Review of AEATF II Paint Hand Wash Removal Efficiency Protocol. March 18, 2014. https://www.epa.gov/sites/production/files/2014-12/documents/science-ethics-review-removal-efficiency-protocol-march-2014.pdf

[2] Parkin, Rebecca T. April 8-9, 2014 Human Studies Review Board Meeting Report. June 25, 2014. https://www.epa.gov/sites/production/files/2014-11/documents/hsrb-final-report-april-2014-meeting.pdf

"Resident of Fresno County" to "Resident of Fresno County and the surrounding area", and revises the randomization and subject selection process to account for two sessions of 5 test subjects on each test day. The second amendment corrects the title and number for the analytical method cited in the protocol.

The first reported deviation was discussed in Section 2.a. above, relating to the failure to publish the recruitment advertisement in the California Advocate. The second deviation noted that diethylene glycol was used instead of dipropylene glycol when preparing the BIT solution. The third deviation reported a failure to collect duplicate control samples at each fortification event. These deviations from the protocol did not impact the health, safety, or rights of subjects.

5. Informed Consent

All participating subjects completed the informed consent process and signed the consent form. The consent form was approved by Schulman IRB on February 9, 2015. Schulman IRB provided certified translations from English to Spanish of the recruitment and consent materials.

Potential candidates who responded to the recruitment advertisement were interviewed by phone to determine whether they met basic criteria. If they were still interested in participating and provisionally qualified, they were invited to Golden Pacific Laboratories for a consent meeting and were instructed to bring a government-issued photo ID. Meetings were held one-on-one with a member of the study team, unless a subject chose to bring a friend or family member. As per the protocol, each person was offered the option to have the meeting conducted in English or Spanish. Three potential candidates requested communications and materials presented in Spanish. Candidates were provided with materials related to the study (consent form, qualification worksheet, product label, and product SDS), and asked to fill out the first part of the qualification worksheet. The researcher conducting the meeting reviewed the qualifications, and if the basic eligibility criteria for the study were met, proceeded to review the informed consent materials, including the "Experimental Subject's Bill of Rights". Researchers encouraged candidates to ask questions throughout the consent process and during the study itself, and reminded candidates that they were free to withdraw from the study at any time. After the consent meeting, those who met the eligibility criteria and were interested in continuing were asked to complete the second part of the qualification worksheet, and to sign and date the informed consent materials to enroll in the study.

6. Respect for Subjects

Subjects' identifying information was kept confidential. This protocol required the testing process to be videotaped, and all photos or videos associated with the study were reviewed to ensure they did not show the subject's face, tattoos, or other identifying features. Subjects were assigned identification numbers, and their names were not revealed in the study report.

Each subject received compensation consistent with the protocol and informed consent document. Compensation was $20 for participating in the consent meeting and $100 for showing up to the test site, regardless of whether they were monitored as a test subject or served as an alternate.

Subjects were informed during the consent meeting and on the day of monitoring that they were free to withdraw at any time without penalty. Several subjects withdrew by not showing up on the day of their scheduling monitoring event or withdrew in advance for personal reasons.

Completeness of Submission

The submission by AEATF and additional materials provided by Schulman IRB satisfy the requirements of §26.1303. A checklist indicating how each requirement has been satisfied is provided in Attachment 2.

Applicable Ethical Standards

The following provisions of 40 CFR 26 Subpart Q define the applicable ethical standards which read in pertinent part:

> **§26.1703**: Except as provided in §26.1706, EPA shall not rely on data from any research subject to this subpart involving intentional exposure of any human subject who is a pregnant woman (and therefore her fetus), a nursing woman, or a child.
>
> **§26.1705**: Except as provided in §26.1706, EPA must not rely on data from any research subject to this section unless EPA determines that the research was conducted in substantial compliance with all applicable provisions of subparts A through L of this part.

In addition, §12(a)(2)(P) of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) applies. This passage reads:

> In general, [i]t shall be unlawful for any person . . . to use any pesticide in tests on human beings unless such human beings (i) are fully informed of the nature and purposes of the test and of any physical and mental health consequences which are reasonably foreseeable therefrom, and (ii) freely volunteer to participate in the test.

Prohibition of research involving intentional exposure of pregnant or nursing women, or of children

40 CFR §26.1703 prohibits research involving intentional exposure of pregnant or nursing women or of children under 18. Pregnancy testing of female subjects on the day of testing was conducted and no pregnant or lactating women were enrolled in the study. All subjects who participated in study AEA08 were at least 18 years old. Therefore, 40 CFR §26.1703 does not prohibit reliance on this research.

Substantial compliance with 40 CFR 26 subparts A through L

40 CFR §26.1705 requires that EPA have "adequate information to determine that the research was conducted in substantial compliance with subparts A through L of this part." Within this range, only subparts K and L are directly applicable to the conduct of third-party research such as this. The AEA08 study was conducted in substantial compliance with subparts K and L.

Compliance with 40 CFR §26 subpart M

As documented in Attachment 2 to this review, the central requirements of 40 CFR §26 subpart M, §26.1303 to document the ethical conduct of the research were addressed.

Compliance with FIFRA §12(a)(2)(P)

The requirement of FIFRA §12(a)(2)(P) that human subjects of research be "fully informed of the nature and purposes of the test and of any physical and mental health consequences reasonably

foreseeable therefrom," and "freely volunteer to participate in the test," was met for this study.

Conclusion

This study reports research conducted in substantial compliance with the requirements of 40 CFR 26 subparts A through L. In its conduct, study AEA08 met applicable ethical standards for the protection of human subjects of research, and requirements for documentation of ethical conduct of the research were satisfied. From EPA's perspective, if this study is determined to be scientifically valid and relevant, there is no regulatory barrier to EPA's reliance on it in actions under FIFRA or §408 of FFDCA. This research will also undergo review by the Human Studies Review Board.

cc: Rick Keigwin
Tim Leighton
Tim Dole

Attachment 1: AEATF actions in response to EPA and HSRB comments on protocol
Attachment 2: §26.1303 Completeness checklist for AEA08 Study
Attachment 3: Additional IRB Minutes (2/2/2015) and IRB Roster

Attachment 1
Ethics Comments from April 2014 HSRB Meeting & AEATF Actions

EPA Comments on AEA08 Protocol	AHETF Actions to Address Comments
Revise the exclusion criteria as follows "Allergies **or sensitivities** to latex paint, soaps, isopropyl alcohol, **BIT, or other chemical-based products**"	Comment was incorporated (p. 76).
Revise the "Test Product" section of the consent form as follows: "The test product contains a ~~chemical~~ **pesticide** known as BIT which helps keep bacteria from growing."	This comment was not incorporated. Per AEATF, the prior section of the Informed Consent describing the purpose of the study to subjects referred multiple times to the "chemical" which would be measured in air and on dermal matrices. AEATF felt that consistency of terminology should be maintained so that subjects would be aware that the "chemical" to be measured was BIT. The sentence in the "Test Product" section went on to state that BIT "helps keep bacteria from growing" to clarify it is an antimicrobial pesticide. The risks section of the Informed Consent was updated to use the word "pesticide."
Revise the "Risks" section of the consent form as follows: "Risk of a reaction to the latex paint **or the pesticide ingredient (BIT) contained in it**."	Comment was incorporated (p. 103).
Incorporate forthcoming guidance from HSRB about how to provide personal exposure results to subjects.	The HSRB did not finalize the report from the HSRB's working group.

HSRB Comments on AEA08 Protocol	AEATF II Actions to Address Comments
Revise protocol to state that "study is not actively recruiting participants from potentially vulnerable populations."	Statement on vulnerable populations was deleted.
Eliminate the statement that "there is little incremental risk associated with [the study]."	Per the Principal Investigator, "the statement was not changed since it was not in the literature that was used to recruit or explain the study to the subjects and therefore would not be used to coerce subjects to participate by minimizing the risk. The statement was to rationalize that even though we would be intentionally exposing human subjects to BIT, which is a pesticide, it was chosen because it has low toxicity and may be lower risk than other pesticides."

HSRB Comments on AEA08 Protocol	AEATF II Actions to Address Comments
Modify discussion of “good health” in the protocol and informed consent document to include definitions of the terms.	Per the Principal Investigator, “the purpose of the "Subject Invitation to Participate" is to initiate communication and schedule an interview with the interested subjects at which time the subject can get informed and ask questions before signing to participate or opting out. The phone screening was kept simple to give general information so subjects can decide if they are interested. The study enrollment section of the informed consent was not changed since the section above it, subject selection, already specified the exclusion criteria detail as HSRB was asking for. The statement "we will ask for you about your general health" was used during the interview as an explanation to the specific questions on the qualification worksheet.”
Update informed consent document to 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.	Per the Principal Investigator, “the protocol was not rewritten to reflect changes because the protocol already stated that a padded surface on the table would be provided. Study personnel reviewed the potential for discomfort and established resting surfaces and practices to eliminate the potential discomfort. Study personnel then simulated the experience of the subjects sitting at the table in the chairs where the subjects would be during the study. Study personnel and the Study Director determined that any possible discomfort would not hold a definable risk to the subjects. At the monitoring event, subjects were informed that if they desired to stand at any time staff would help them out of their chairs and back into them. All subjects completed the 45 minutes of drying time without any indication of discomfort.”
The risk of using a glass capillary tube, which can have rough ends and can shatter, should be noted in the protocol and informed consent document. Alternatively, consider using another means of spreading the test material.	Protocol revised to use “glass stirring rod with rounded annealed ends” for spreading the test substance on subjects’ palms.
The Board 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.	Comment was addressed. Researchers completed training on human subjects protection within three years of study initiation.

Attachment 2
§ 26.1303 Checklist for Completeness of AEA08 Submitted for EPA Review

Any person who submits to EPA data derived from human research covered by this subpart shall provide at the time of submission information concerning the ethical conduct of such research. To the extent available to the submitter and not previously provided to EPA, such information should include:

Requirement			Y/N	Comments/Page References
(a) Copies of all of the records relevant to the research specified by §26.1115(a) to be prepared and maintained by an IRB	§1115(a)(1): Copies of • all research proposals reviewed, • scientific evaluations, if any, that accompany the proposals, • approved sample consent documents, • progress reports submitted by investigators, and reports of injuries to subjects.		Y	
	§1115(a)(2): Minutes of IRB meetings which shall be in sufficient detail to show • attendance at the meetings; • actions taken by the IRB; • the vote on these actions including the number of members voting for, against, and abstaining; • the basis for requiring changes in or disapproving research; • a written summary of the discussion of controverted issues and their resolution.		Y	
	§1115(a)(3): Records of continuing review activities.		Y	
	§1115(a)(4): Copies of all correspondence between the IRB and the investigators.		Y	
	§1115(a)(5): • A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; • any employment or other relationship between each member and the institution		Y	
	§1115(a)(6): Written procedures for the IRB in the same detail as described in § 26.1108(a) and § 26.1108(b).		Y	EPA received this previously.
	§1115(a)(7): Statements of significant new findings provided to subjects, as required by § 26.1116(b)(5).		n/a	
(b) Copies of all of the records relevant to the information identified in §26.1125(a)-(f)	§1125(a) A discussion of:	(1) The potential risks to human subjects;	Y	
		(2) The measures proposed to minimize risks to the human subjects;	Y	
		(3): The nature and magnitude of all expected benefits of such research, and to whom they would accrue;	Y	
		(4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and	Y	
		(5) The balance of risks and benefits of the proposed research.	Y	
	§1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB.		Y	
	§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.		Y	
	§1125(d): A description of the circumstances and methods proposed for presenting information to potential human subjects for the purpose of obtaining their informed consent.		Y	
	§1125(e): All correspondence between the IRB and the investigators or sponsors.		Y	
	§1125(f): 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.		Y	
(c) Copies of sample records used to document informed consent as specified by §26.1117, but not identifying any subjects of the research			Y	
(d) If any of the information listed in paragraphs (a) through (c) of this section is not provided, the person shall describe the efforts made to obtain the information.			n/a	