EPA Human Studies Review Board (HSRB)
July 21, 2022 Meeting Minutes

July 21, 2022 EPA Human Studies Review Board Meeting Minutes

Committee Members: (See EPA HSRB Members List – Attachment A)

Date and Time: Thursday, July 21, 2022, 1:00 to 5:00 pm EDT.

Location: Via Zoom Meeting

Purpose: The HSRB provides advice, information and recommendations on issues related to scientific and ethical aspects of human subjects research.

HSRB Website: https://www.epa.gov/osa/human-studies-review-board

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Thursday, July 21, 2022:

A. Meeting Topic and Charge Questions

Topic: Ladics, Gregory S. BIT: Repeated insult patch test, Laboratory final report number 90RC-181. Performed by Hill Top Research, Inc. Sponsored by the Rohm and Haas Company. Submitted to EPA by DDP Specialty Electronic Materials, US 5, LLC. January 30, 1991. 42 pages. MRID 51171302.

Charge to the Board – Science: Is the research described in the unpublished study "BIT: Repeated insult patch test, Laboratory final report number 90RC-181" scientifically sound, providing reliable data?

Discussants: Thomas Lewandowski, Ph.D.

Charge to the Board – Ethics: Does available information support a determination that there is no clear and convincing evidence that the conduct of the research was fundamentally unethical or deficient relative to the ethical standards prevailing at the time the research was conducted in a way that placed participants at increased risk of harm or impaired their informed consent?

Discussants: Philip Day, Ph.D.

B. Convene Public Meeting

Tom Tracy, Designated Federal Officer, EPA Human Studies Review Board (HSRB), Office of the Science Advisor, Policy and Engagement (OSAPE)

Mr. Tom Tracy, Designated Federal Official (DFO) for the HSRB, called the meeting to order at 1:00 p.m. EST. He noted upcoming membership changes effective August 31st. He stated that Mark Aulisio and Janice Britt will be leaving HSRB. Since the terms of the chairs conclude before the review of the study ends, Mr. Tracy has asked Lisa Corey and Julia Sharp to act as co-chairs. He also mentioned 7-8 new members will be proposed because of waning membership. He introduced the meeting, outlined the Federal Advisory Committee Act (FACA) procedures, and performed a roll call of the meeting participants. The following members and observers were present:

HSRB members	Jennifer Cavallari, Sc.D., University of Connecticut (Chair) Alesia Ferguson, Ph.D., North Carolina A&T State University (Vice Chair) Mark Aulisio, Ph.D., Case Western University Philip Day, Ph.D., University of Massachusetts, Chan Medical School George Milliken, Ph.D., Milliken Consultants Julia Sharp, Ph.D., Colorado State University Albert J. Allen, M.D., Ph.D., Eli Lilly Eun Um, Ed.D., AMSTAT Consulting Lisa Corey, Ph.D., Intertox, Inc. Thomas Lewandowski, Ph.D., Gradient Janice Britt, ToxStrategies
EPA staff members	Michelle Arling, EPA, Office of Pesticide Programs (OPP) Tom Tracy, EPA, Office of Science Advisor, Policy and

	Engagement (OSAPE) Tim McMahon, EPA, OPP Judy Facey, EPA, OPP Taylor Lass, EPA, OSAPE Monique Tadeo, EPA, Program in Human Research Ethics and Oversight (PHREO) Alexander Kliminsky, EPA, Office of Chemical Safety and Pollution Prevention (OCSPP) Timothy Dole, EPA, OPP
Members of the public, representatives of research sponsor and research team:	Sam Whately, ICF, Contractor Support Julia Finver, ICF, Contractor Support Sheerin Shirajan, ICF, Contractor Support

Mr. Tom Tracy reviewed Zoom Meeting platform tools and features and stated the purpose of the meeting was to review the research by Ladics, Gregory S. BIT: Repeated insult patch test, Laboratory final report number 90RC-18. He noted the minutes of the meeting, and a report will be prepared, certified, and posted on the EPA HSRB SharePoint website within 90 days of July 21, 2022.

C. Welcome and Virtual Meeting Operations

Jennifer Cavallari, Sc.D., HSRB Chair

Jennifer Cavallari welcomed everyone and thanked everyone for her time as Chair of HSRB. She reviewed the agenda and asked participants to save any discussion elements for later in the meeting. Dr. Cavallari further instructed participants to state their name before speaking, and for board members to use the reaction features in Zoom to vote, using the green check as a "yes" and the red X as a "no." Additionally, she asked if there were any further questions before starting the meeting.

D. Updates from OPP

Michelle Arling, J.D., Office of Pesticide Programs

Michelle Arling expressed her gratitude for Jennifer Cavallari as Chair and Alesia Ferguson as Vice Chair and thanked them for their time during their tenure. She stated there will be a full agenda for the October meeting which will be held over the course of three days.

E. EPA Science Review Highlights

Tim McMahon, Ph.D., Office of Pesticide Programs

Dr. Tim McMahon introduced himself and his fellow colleague, Dr. Judy Facey. He stated he would present one human study that examined dermal sensitization, also termed allergic contact dermatitis, for the chemical benzisothiazolinone (BIT), specifically the potential of BIT to cause elicitation of dermal sensitization in human volunteers who were intentionally exposed.

Dr. McMahon discussed the outline for his presentation and started with an introduction and purpose for the study. Dr. McMahon would also provide a background on allergic contact dermatitis evaluation, BIT, and the current risk assessment approach. Lastly, he would summarize the BIT human study that the Agency plans to use in support of deriving a point of departure for dermal sensitization to BIT.

Dr. McMahon presented slide 3, Introduction and Purpose, of his presentation. The Agency published draft risk assessments (DRAs) in support of the registration review of five isothiazolinone chemicals in

May 2020. The assessments included a quantitative assessment of dermal sensitization hazard. The quantitative dermal assessments were based on the use of validated in vitro and in silico methods for the derivation of points of departure for use in dermal risk assessments for these chemicals. Dr. McMahon explained that following the publication of the DRAs, there was a 6-month public comments period, which closed November 2020. He mentioned the Agency is in the process of responding to the public comments. Additionally, after the publication of the DRA for BIT, the Agency received and reviewed an intentional dosing study conducted in human volunteers with BIT examining dermal sensitization potential, and the Agency is seeking the recommendations of the HSRB on the scientific and ethical acceptability of this study.

Dr. McMahon presented slide 4 on the Background on Allergic Contact Dermatitis (ACD). He stated ACD is characterized by two phases: induction and elicitation/challenge. Induction is an exposure of sufficient magnitude and/or duration to activate specific immune mechanisms resulting in the acquisition of sensitization by creating immune memory. The elicitation/challenge phase is where the response induced in sensitized individuals upon subsequent exposure to the allergen. Dr. McMahon states a familiar example of the elicitation or challenge phase is the visual response one may experience from a poison ivy response.

Dr. McMahon moved on to slide 5 where he discussed the differences between irritation versus sensitization. He stated that both irritation and sensitization are characterized by edema and erythema; however, irritation is an immediate reaction, whereas a sensitization reaction can take anywhere from 24 to 72 hours. An irritation response happens on first exposure and does not involve immune memory, whereas there is no response on the first exposure for sensitization without immune memory.

Dr. McMahon presented slide 6 about Quantitative Assessment of ACD Hazard and Risk and explained dermal sensitization risks are typically communicated through product labeling in which labels on the product warn that it may cause dermal sensitization. He noted that the use of antimicrobial pesticides for preservation of certain materials, e.g., plastics, wood, and paints, presented a challenge for the Agency to communicate to the public of the presence of potential dermal sensitizing chemicals. These materials do not bear label statements indicating the potential for dermal sensitization; thus, hazard and risk cannot be communicated through labeling. In these instances, quantitative methods provide a means for assessing sensitization potential and risk for these types of pesticide uses. Quantitative methods are used to determine an exposure level that does not produce an adverse effect.

Dr. McMahon presented slide 7 on Development of Quantitative Methods. The Agency's interest in developing quantitative methods for dermal sensitization hazard and risk assessment for pesticide chemicals goes back to 2004, where the available quantitative methods were presented to the Agency's Federal Insecticide, Fungicide, Rodenticide, Act Science Advisory Panel (FIFRA SAP). He explained FIFRA SAP is an independent advisory panel composed of biologists, statisticians, toxicologists, and other experts, who provide independent scientific advice to the EPA on a wide range of health and safety issues related to pesticides. Additionally, he stated hexavalent chromium, which is a strong dermal sensitizer and was used as a preservative component in pressure-treated wood, was presented to the SAP as a case study using in vivo quantitative approaches based on results of human studies. In particular, the results of the Repeat Open Application Test Method (ROAT) were presented, and eventually used for assessing risk from dermal exposure to hexavalent chromium in pressure-treated wood.

Dr. McMahon presented the SAP recommendations in slide 8, which stated the SAP agreed that quantitative approaches to assessment of dermal sensitization risk were appropriate. Several methods at that time were considered scientifically sound, including the ROAT and Local Lymph Node Assay

(LLNA) as these approaches measure dose-response using a dose/unit area metric. Furthermore, SAP acknowledged that human data are preferable for establishing a 'safe' area dose over animal data, if huma data were to be available. The panel also agreed the threshold for induction is considered to be higher than that required for elicitation. Therefore, establishing a level below the threshold for elicitation would also be protective of induction, which is an agreement with scientific literature (Kimber et al., 2003). Dr. McMahon noted that since 2004, scientific methods for assessment of dermal sensitization have advanced, the use of validated in vitro and in silico test methods have begun to allow a quantitative determination of dermal sensitization induction thresholds. These methods have been applied to the other isothiazolinone chemicals in the Agency's published draft risk assessments.

Dr. McMahon discussed the current approach for BIT on slide 9. He explained the Agency derived a point of departure in the DRA using an in vitro induction threshold value of 85 µg/cm ² based on application of the Shiseido Artificial Neural Network defined approach to results from three internationally harmonized in vitro test methods- the direct peptide reactivity assay (DPRA), human cell line activation test (h-CLAT), and the KeratinoSens™ assays. An uncertainty factor (UF) of 100x was applied to the induction threshold value derived from these results from a 10x factor applied for extrapolation from animals to humans and a10x factor applied for human variability. The 100x factor was based on the use of an induction value, and the use of in vitro/in silico assays to characterize human risk. The Agency intends to use the results of a submitted human study and a reduced UF to refine the dermal risk assessment for BIT.

Dr. McMahon explained the background of BIT in slide 10. BIT, a chemical in the isothiazolinone class, has been demonstrated to be a positive sensitizer in animal studies and in vitro studies. A recent publication by King, et al., demonstrated an increase in prevalence of Allergic Contact Dermatitis (ACD) to BIT from 2014 to 2019 in patch tests conducted in humans. BIT has several EPA registrations as an antimicrobial pesticide in treated article applications where repeated dermal contact can occur (e.g., laundry/dishwashing detergent, household cleaning products, metalworking fluids, carpet cleaner, paints, and paper/ paper products).

Dr. McMahon explained the Agency examined the Incident Data System (IDS) on May 10th, 2022, for reports of human incidents involving BIT and dermal reactions. The IDS contains reports submitted to the Agency under the 6(a)(2) provision of FIFRA, and from voluntary reports such as from the National Pesticide Information Center (NPIC) and from other federal agencies. For BIT, a total of six human incidents involving products containing BIT were found between from January 1999 to May 2022. The incidents were reported as moderate, where dermal irritation/ erythema/ pain/ rash were reported in workers from product spills on the skin.

Dr. McMahon noted in addition to the Agency's published assessment on BIT, the Scientific Committee on Consumer Safety (SCCS) also published an opinion on BIT. The SCCS is one of three committees that provide the European Commission with the scientific advice it needs when preparing policy and proposals relating to consumer safety, public health and the environment. For BIT, the SCCS's published stated that, "Benzothiazolinone is known to be a sensitizer in man and has induced sensitization at [levels of approximately] 20 ppm from use of gloves. There is no information on what may be safe levels of exposure to benzisothiazolinone in cosmetic products from the point of view of sensitization."

As Dr. McMahon alluded to previously, he stated the Agency believes that dermal sensitization is a more appropriate point of departure. He explained irritation is a reversible effect; sensitization reactions can occur over a lifetime from each exposure to a sensitizing chemical. BIT is a known dermal sensitizer

present in several EPA-registered products. A similar approach was presented to the HSRB for assessment of dermal sensitization hazard and risk for isothiazolinone chemicals methyl- and chloromethyl- isothiazolinone in 2017. Dermal sensitization has been used as the point of departure for assessment of dermal risk to the isothiazolinone chemicals under registration review.

Dr. McMahon stated the Agency is proposing to use the Ladics study[1] for determination of the point of departure for BIT in dermal risk assessments, as well as a reduced uncertainty analysis in the dermal risk assessment. A second study[2] (Basketter, et al.) was submitted to the Agency for BIT that compared the relative sensitizing potency of three isothiazolinone biocides. However, Basketter contained only summary information and the full study was not made available to the Agency.

Dr. McMahon introduced the BIT Human Study, which was the focus of the July 21st, 2022 meeting. The purpose of the study was BIT was to examine the potential of BIT to induce contact sensitization in 121 human subjects and to observe any potential irritation effects from dermal exposure to BIT. The initial subject design involved 121 subjects, with 10 subjects eventually withdrawing. A brief medical history and informed consent to participate in the study was obtained from each test subject.

Dr. McMahon listed the determining factors for why subjects were excluded from the study:

- History of poor health or insulin-dependent diabetes.
- History of bilateral mastectomy or any mastectomy within the past year.
- History of active skin cancer.
- Current skin disease, which may contraindicate participation, including psoriasis or active. eczema, even if currently controlled through medication.
- History of participation in a Draize type patch test within the past three months.
- Current use of anti-inflammatory steroids or antihistamine medications.
- Severe asthma.
- Use of topical drugs at site of patching.
- In addition, any subject absent more than once during the induction phase or at any time during the challenge week was withdrawn from the study.

Slide 17 of Dr. McMahon's presentation showed a representation of the Human Repeat Insult Patch (HRIPT) study design Patch Test with an image of a human back, with three white, rectangle patches covering the site where the chemical was placed. He explained in this general design, the chemical or chemicals can be applied to several small defined areas as a single or repeated exposure, and then are typically covered with a bandage. Dr. McMahon mentioned the image depicts a test that was done on the human's back, but the BIT study was done on the participant's forearm.

In Slide 18, which focused on the BIT study protocol- HRIPT design, Dr. McMahon stated the participants were divided into two groups. For the induction phase, group 1 participants (subjects 1-60) received nine induction applications of 500 ppm BIT in Rhoplex AC-64 vehicle three times a week for three weeks. Group 2 participants (subjects 61-121) received nine induction applications of 1000 ppm BIT in Rhoplex AC-64 vehicle three times over week for three weeks. He explained all participants also received the undiluted vehicle (Rhoplex AC-64, an acrylic emulsion for water-based paints) three times per week for three weeks. These applications were made directly to the lateral surface of the left and

[1] Ladics, G.S. (2020): BIT repeated insult patch test. Report No. NB-200034-1730. Laboratory Final Report No. 90RC-181. Unpublished. MRID 51171302

[2] David Basketter, et. Al., and published in Contact Dermatitis40: 150-154, 1999

right upper arm in all participants. Following the application, samples were allowed to air dry for 10 minutes and then were covered with a semi-occlusive patch.

Dr. McMahon explained the elicitation (or challenge) phase of the study. A two-week rest period followed the last induction application. The challenge application was made to each participant at a site adjacent to the original induction application site. Contact time was 24 hours for the challenge application. Simultaneous application to the original site used for Induction Application No. 1 was also made concurrently with the challenge at the site. The challenge application concentrations of BIT were the same as induction concentrations.

Dr. McMahon then discussed the scoring scale on slide 20 which ranged from 0 to 5:

- 0 - No evidence of any reaction
- 1 - Reaction readily visible but mild unless letter grade appended. Mild reactions include weak but definite erythema, and weak superficial skin responses such as glazing, cracking, or peeling.
- 2 - Definite papular response
- 3 - Definite edema
- 4 - Definite edema and papules
- 5 - Vesicular/bullous eruption

Dr. McMahon stated if the letter "E" is appended to the numerical grade, it documents the presence of strong erythema at the patch site. If the letter "F" is appended to the numerical grade, it documents the presence of strong effects on superficial layers of the skin. These include fissures, a film of dried serous exudate, small petechial erosions and/or scabs. Lastly, if the letter "S" is appended to the numerical grade, it documents the presence of a reaction spreading beyond the test site.

Dr. McMahon explained the results of this study, where 111 of the 121 test subjects completed the HRIPT protocol. In the induction phase: 6 of the 111 subjects showed a Grade 1 reaction to the vehicle. Three subjects showed consecutive or sporadic Grade 1 reactions to BIT at 27.8 µg/cm², and 6 subjects showed sporadic or consecutive Grade 1 reactions to BIT at 55.6 µg/cm². He stated these results indicate there was some irritant response in the induction phase, as well as response to the vehicle. In the challenge phase, outlined on slide 23, two subjects showed positive reactions to the vehicle control during the challenge phase. One subject in the 7.8 µg/cm² group showed a Grade 1 response on challenge, and one subject in the 55.6 µg/cm² group showed a Grade 2 response on challenge. The same subjects also showed positive (Grade 1) reactions to the vehicle. It was concluded in this study that BIT is not a dermal sensitizer up to the 55.6 µg/cm² concentration.

Dr. McMahon listed the strengths and limitations of the BIT study on slides 24 and 25.

Strengths:

- Both males and females are represented in the study.
- Sufficient sample size.
- Two doses were tested.
- A vehicle control was included in the study design.
- A point of departure (POD) could be estimated from the data.
- The skin loading used in this study aligns with potential skin loading expected for registered pesticidal uses of BIT, where loading rates range from 0.23 to 55.6 µg/cm² as published in the Agency's BIT DRA.

Limitations:

- Concentrations tested were not high enough to establish an elicitation threshold.
- Males and females were not represented equally.
- No statistical tests were performed by the authors in this study. The Agency conducted its own statistical analysis of the data.
- Reactions were observed from vehicle application.
- An explanation for the use of the Rhoplex AC-64 as a vehicle was not provided.
- Information on the potential effect of this vehicle on absorption of BIT through the skin was not provided.

Dr. McMahon identified the Conclusions and Impact on Risk Assessment of the BIT Study on slide 26. In the Human Repeat Insult Patch test protocol used in this study, BIT was observed to be negative for elicitation of dermal sensitization up to a skin concentration of 55.6 µg/cm². Dr. McMahon reiterated the Agency agrees with this determination. The study is scientifically sound, used a top dose that resulted in minor irritation in only a few of the subjects, and provided information for determination of a POD for assessment of the dermal sensitization hazard of BIT. The Agency's own statistical analysis was in agreement with the POD selected for BIT from this study.

Finally, he provided the question to the HSRB: Is the question described in the unpublished study, "BIT repeated insult patch test. Report No. NB-200034-1730. Laboratory Final Report No. 90RC-181, scientifically sound, providing reliable data?

Dr. McMahon stated that his presentation had concluded and thanked the participants for their time.

F. Board Questions of Clarification

Jennifer Cavallari, Sc.D., HSRB Chair

Dr. Jennifer Cavallari asked if there were any questions of clarification from the board. She stated as a courtesy, she would let Tom Lewandowski and Lisa Corey, the discussants of the meeting, go first. Dr. Lewandowski stated he had no questions. Dr. Cavallari asked Dr. Corey if she had any questions.

- **Lisa Corey**: I know you mentioned having both males and females represented, but I was also wondering if you knew if there were any differences that were racially defined in skin sensitization, like would there need to be any discussion of what the make-up of the study population was and if that had any relevance on the rates thar you were seeing?
- **Tim McMahon**: Thank you for that question. I am not aware specifically of study population results. As far as I can recall, this was not in the report, but I cannot confirm unless I am able to go back and find that information in the study report itself. That is a good question.
- **Lisa Corey**: I don't think it is in the study report. This may come out in the recommendation, but in the EPA report it might be useful to have a sentence saying that there aren't differences that are defined racially, or maybe there are.
- **Tim McMahon**: Generally, from what I know, with age there isn't, but I cannot completely address the issue of race, which of course, may be in some other publications. It doesn't seem to be in this particular one.
- **Judy Facey**: That was not in the study report.
- **Tim Dole**: We had that literature article about contact dermatitis, maybe that has something.
- **Lisa Corey**: Oh, good idea. Okay, that's right. I also was pretty sure that wasn't in the study report, but like I said that might come in my recommendation later, just to acknowledge it.

Dr. Cavallari asked if there were any more questions of clarification from the board.

- **Tom Lewandowski**: I think you said one of the limitations was that the dose wasn't high enough to provoke an elicitation response, and actually those doses are consistent with patch test recommendations. You wouldn't expect an elicitation response unless people had already been induced and I guess the assumption would be that from the general population people wouldn't be induced, but I guess I wasn't entirely understanding that limitation, maybe you could explain that more?
- **Tim McMahon**: The study did have an induction phase where people followed a protocol that is typically used for induction of sensitization in the patch test. So, the doses that were used, you either don't want to see any irritation, or you only want to see mild irritation. We had some irritation reactions, which might have been a little bit confounded by the vehicle, but it did have some irritation without anything severe, and upon challenge you only saw something that was similar to what they saw in induction, and they did not report a definitive sensitization appearance type response. In that sense, meaning a limitation would be only if they had tested higher if they would have wanted to drive this reaction to see exactly where we would start looking and seeing a definitive sensitization skin response and I think they were right there, but there were only two doses in the study, but that said I have a feeling if they used higher induction doses they might have gotten significant irritation which might have confounded the results of the elicitation phase.

Dr. Cavallari asked the HSRB if there were any more questions of clarification.

- **Janice Brit**: You said that this has been used in other products in the pesticide and antimicrobial area, so have other carrier agents or other material it has been mixed with, has that affected the level or degree of any kind of an irritation, assuming that is used at similar concentrations in the products?
- **Tim McMahon**: That is a good question and something I discussed recently with my colleague, Tim Dole. This particular vehicle is used, in paint, so one might surmise that this is directly applicable to someone that is exposed to paint that's preserved with BIT. The other information that we have was published as a result of traditional animal tests or as I mentioned the in vitro or in silico tests, so I am guessing that there are other vehicles or formulations besides this, but I can't say definitively unless Tim might know.

Dr. Cavallari asked if there were any additional questions of clarification from the board. There were none. Dr. Cavallari stated she would turn it over to Michelle Arling for the EPA Ethics Review Highlights.

G. EPA Ethics Review of Highlights

Michelle Arling, Ph.D., Office of Pesticide Programs

Dr. Michelle Arling presented the outline of the ethics review that was conducted in the study on slide 2 of her presentation. The ethics review was based on the memo provided to the HSRB. The memo is primarily based on the study report, information from the data submitter, and a conversation with Dr. Rimes, the principal investigator on the study. Dr. Arling referenced specifically what information was from Dr. Rimes, otherwise it was from the study report.

On slide 3, Dr. Arling noted there were 121 individuals enrolled in the study at the outset and 10 withdrew, which left a total of 111 subjects who completed the study. She explained the demographics of the subjects: 85 were female and 26 were male, and ages ranged from 18 years old to over 60 years old. Candidates as young as 16 years old were permitted to enroll with their parents' consent, but the

youngest subject was 18 years old.

On slide 4, Dr. Arling explained the eligibility criteria and listed why subjects would be excluded from the study:

- Any skin condition or disease that would be exacerbated by participation in the study and exposure to irritants and sensitizers.
- Any active skin cancer, history of mastectomy, diabetes, or poor health.
- Use of anti-inflammatory or antihistamine medications.
- Use of topical drugs at the site of the testing.
- No pregnant or lactating women.

She stated the study report did not cover the enrollment of pregnant or lactating women, however, Dr. Arling indicated that Dr. Rimes confirmed that the lab HillTop's practice was to exclude pregnant and nursing women from that type of research. Dr. Rimes explained during the consent process they explained the requirement, that women were not allowed to be in the study if they were pregnant or lactating and were told to use birth control for the duration of the study. Additionally, women were told to inform the study staff immediately if they became pregnant during the study, at which point they would be removed immediately from the study.

Dr. Arling referenced the consent form on slide 5. She indicated candidates were invited to read the printed consent form prior to their enrollment, they were offered the option to ask any questions before they signed the form. The consent form covered the study's purpose and conduct, the type of test substance, the risks of participation, and compensation for enrolled subjects. The consent form made clear that subjects were free to withdraw at any time and the study report notes that all subjects provided written informed consent prior to participating.

Dr. Arling moved on to discuss the risks and risk minimization on slide 6. Dr. Arling mentioned that BIT can cause skin irritation and sensitization. She pointed out this was a known risk going into the study. She explained how risks were minimized through selection of test substance levels based on animal testing data, eligibility criteria, and study stopping rules to minimize the risk to subjects. She provided examples of study stopping rules, such as moving the test site during the induction phase if a strong reaction was observed and discontinuing any applications or participation in the study following a third strong reaction during the induction phase. Dr. Arling added there were no direct benefits to the subjects participating in this study. The company would benefit from data that supports the use of its product and accurate data on the level of BIT that could induce skin sensitization could be used to inform risk assessments. The potential societal benefits were establishing a dose of BIT that could be used safely in products. Dr. Arling observed that the potential benefits outweighed the risks which were effectively minimized.

Next, Dr. Arling presented slide 7, Respect for Subjects, that subjects were free to withdraw at any time during the study, as represented by the 10 subjects who withdrew. Additionally, subjects were paid for participation. Dr. Arling addressed that the subject's privacy was protected by using numbers to identify subjects and securing all personal data. Medical care was provided to subjects throughout the study in the case that they had an adverse reaction. Lastly, she stated that workers' compensation coverage was available if subjects were unable to work due to their participation in the study.

Dr. Arling discussed the Independent Ethics Review on slide 8. She noted there was no record of an independent ethics review provided to EPA, either in the study report or additional information submitted with the study report. Furthermore, the report itself was conducted according to standard

protocol. She explained in her conversation with Dr. Rimes, he confirmed that at the time that the research was conducted, the Hill Top Research's practice was to conduct an independent ethics review of all repeated insult patch test and skin sensitization studies. Dr. Rimes also confirmed they had their own institutional review board that was independent of the company and the investigators, and this type of research was run though the Independent Review Board (IRB) before subjects were enrolled.

Additionally, on slide 9, Dr. Arling covered Substantive Acceptance Standards and noted the parts of the human studies role that govern EPAs consideration of human research. These standards are:

- Prohibits reliance on data involving intentional exposure of pregnant or nursing women or of children.
- Prohibits EPA reliance on data if there is clear and convincing evidence that:

  1. Conduct of the research was fundamentally unethical; or

  2. Conduct of research was deficient relative to the ethical standards prevailing at the time the research was conducted in a way that placed participants at increased risk of harm or impaired their informed consent.

- FIFRA: makes it unlawful to use a pesticide in human tests without fully informed, fully voluntary consent.

Dr. Arling explained on slide 10 whether or not the research being discussed was in line with prevailing ethical standards. These ethical standards included the Declaration of Helsinki, the Nuremburg Code, and the Belmont Report. From these documents, Dr. Arling listed the relevant criteria:

- Research is scientifically sound and conducted by qualified personnel
- Clear purpose and protocol reviewed by an IRB
- Benefits must outweigh the risk to subjects; risks to subjects must be minimized
- Participation is voluntary
- Subject selection in equitable
- Subjects are given informed consent and have the freedom to withdraw
- Subjects' confidentiality and privacy are maintained

Then, Dr. Arling presented her findings on slide 11 using the framework of ethical standards from the aforementioned documents. She found that:

- All subjects were adults.
- No evidence that pregnant or nursing women were enrolled.
- All subjects consented in writing.
- All participation was voluntary, and subjects were free to withdraw at any time.
- Risks to subjects were minimized and outweighed by the potential benefits of the research.

Additionally, Dr. Arling mentioned although there was no record of IRB review, Dr. Rimes confirmed that a review likely occurred. Dr. Arling stated that EPA's position is that a lack of documentation does not indicate deficient ethical conduct of the research.

In conclusion, Dr. Arling indicated through the available information, there is no clear and convincing evidence that the conduct of the research was fundamentally unethical or deficient relative to prevailing ethical standards in a way that would have impaired subjects' informed consent or placed them at increased risk of harm.

Lastly, Dr. Arling posed the charge question on slide 13, "Does available information support a determination that there is no clear and convincing evidence that the conduct of the research was fundamentally unethical or deficient relative to the ethical standards prevailing at the time the research was conducted in a way that placed participants at increased risk of harm or impaired their informed consent?"

H. Board Questions of Clarification

Jennifer Cavallari, Sc.D., HSRB Chair

Dr. Jennifer Cavallari gave the first opportunity for questions of clarification to Dr. Philip Day who led the ethics review for the July 22, 2022, meeting.

- **Philip Day**: Were you able to locate the amount that participants were compensated or incentivized for this study?
- **Michelle Arling**: I wasn't. The consent form that is in the...
- **Philip Day**: Yeah, it just says they were compensated. It doesn't give a number that I can find. Okay, that is it. I don't think there is any evidence of coercion without documentation, it doesn't imply that there was. I was just curious if I had overlooked it.

Dr. Cavallari asked if there were any further questions. There were none. She then asked Tom Tracy to guide those in the meeting through the public comments.

I. Public Comments

Mr. Tracy stated there was one public comment from Ms. Sage Walter. Ms. Walter thanks everyone for the reviews of the science and ethics of the study. She reiterated what was already shared in Dr. McMahon and Dr. Arling's presentations but wanted to give her comments as the study submitter and owner. Ms. Walter explained the objective of the study was to evaluate two concentrations of BIT for the induction of contact sensitization and to report any irritation observed with the test material. She added that the goal of the study is to determine a concentration relative to use of BIT, which will not produce sensitization induction in a previously unsensitized population.

Ms. Walter reiterated that the study was not meant to determine an elicitation concentration as it would certainly be unethical to induce sensitization in individuals in order to measure an elicitation concentration. Also, elicitation would not to be an appropriate endpoint for setting exposure limits to our knowledge. Regulatory bodies worldwide consider induction, rather than elicitation, for setting concentration limits since induction is a chemical specific value, whereas elicitation is variable based on induction concentration, duration of exposure, and other factors. And in individuals already sensitized to a chemical, we would want to use proper warnings and awareness to avoid any continued exposure, eliminating concern for elicitation in those already sensitized.

She continued on to state that the induction concentration of 27.8 µg/cm² and 55.6 µg/cm², or 500 and 1000 ppm were used, which were doses similar to the current and proposed label limits for BIT, therefore the concentration levels were product relevant. Ms. Walter added that 111 subjects completed the study and there was no evidence for contact sensitization at either dose level used. The data provided a no observed effect level (NOEL) of 55.6 µg/cm² for BIT in humans. Ms. Walter highlighted that they consider this study to be of great value in EPA's risk assessment for use of BIT as the study allows derivation of no expected sensitization induction level (NESIL) based on reliable human data. That NESIL is the benchmark by which exposure should be compared to. For defining the NESIL, use of

human data would be the gold standard and should be considered more reliable than use of animal or in vitro data.

Further, Ms. Walter stated the study is valuable in that use of the human data will allow significant modification of the uncertainty factors in the EPA's risk assessment to remove the uncertainty factor associated with interspecies variation as no species-to-species extrapolation is then needed. Ms. Walter added overall, the study is important for setting the NESIL and uncertainty factors for the dermal sensitization endpoint for BIT to appropriately protect the general population from sensitization induction risk from use of BIT in registered use patterns. Then, Ms. Walter recognized the ethical considerations and how they were thoroughly described by Dr. Arling. She repeated that the study was conducted by Hilltop Research, which at the time was Roman Hass Company. Now, the study is owned by Linksys. She mentioned the study investigators sought and obtained informed consent from participants. Although it was not documented in the report, it is assumed that ethical review was obtained. Additionally, no ethical concerns for this study on BIT were identified and there had been no unnecessary duplication of studies. Walters reiterated that the study was scientifically important for the protection of the human population for the registered uses of BIT.

Mr. Tracy thanked Ms. Walter and asked if there were any further comments or questions for Ms. Walters. There were none. Mr. Tracy turned it back to Dr. Cavallari.

J. Break

K. Board Discussion

Jennifer Cavallari, Sc.D., HSRB Chair

Dr. Cavallari welcomed everyone back and held a quick roll call for the HSRB board. Dr. Cavallari then opened the floor for questions from the science discussants, Dr. Thomas Lewandowski and Dr. Lisa Corey.

- **Thomas Lewandowski**: Thank you Jennifer. I will review the study and Lisa will provide additional points.
    - I agree with most of the EPA's concerns and the overall opinion that the study is scientifically reasonable. One concern is there was no assessment of the stability of the test substance. As a multiple dose study, the test substance could have degraded in potency over time. However, isothiazolinones are used as antimicrobials in consumer products to prolong shelf life. Although stability was not characterized, it might not be an issue. We can consider this a concern that I dismissed.
    - Additionally, no documentation was provided concerning the training of staff tasked with examining the participant's skin. It is not unusual for an older study to not call this out in the report. Hilltop is a well-recognized organization in this field of work, so there is no reason to question if the staff being inappropriately trained or insufficiently trained.
    - Another concern is that Roflex A60 AC 64 was used as the vehicle and is this chemical is an emulsion used in latex paints. It is unclear whether an emulsified vehicle would affect BIT's bioavailability or skin permeability, such as the potential of the molecule being complexed with the emulsion components. In the case that this study is used to support determination, the EPA must consider the matrix being used for EPA's application.
    - I noted that the participant population had 3:1 female-to-male ratio. Generally, females do have higher incidence of skin reaction than males. The ratio biases the study towards

precautionary and addresses a more sensitive group of individuals. This seemed appropriate given the concern for skin sensitization.
    - I addressed the concentrations tested as consistent with current patch test recommendations earlier, and the concentrations were not unreasonably low nor biased towards no response.
    - From my perspective, there was a lack of clarity in what the EPA statistical assessment intended to do. Some parts discussed looking for a threshold of sensitization, but it was looking for a threshold of irritation instead. The EPA's document needs to be clarified and check for consistency.
- **Lisa Corey:** I don't have many comments, the study is straightforward, and the results are consistent with what is presented.
    - I agree with Tom's concerns on whether vehicle choice accurately represents current and future use of BIT. There should be discussion on if vehicle choice could impact prospective usage. We can use additional literature for this discussion.
    - There should be a discussion surrounding the applicability of different populations for sensitization. The sex and age of the population are known, but population descriptions besides those are unknown. The EPA's final report should discuss any expected differences between demographic groups for future use.
    - The EPA reported this study as a weight-of-evidence approach. I agree with this, but we are also discussing whether this study could be used as a good POD. I recommend that the EPA keep this study as a weight-of-evidence approach in the report and not fully rely on this study alone for risk assessment decisions.

There were no further comments or questions for the science discussants.

Dr. George Milliken then discussed the statistics of the study.

- **George Milliken:** The study did not conduct statistical analyses but discussed the 3-4 patients who reacted to the exposure.
    - There was no comparison between the treated and controlled groups. The EPA's analyses were appropriate to the data and provided more analyses than usual because EPA was looking for any relationship between the treated and controls. No new relationships were identified.
    - One statement from the FDA Review Report on page 14 stated the study used a "study population" of 111 test subjects. We do not have a population; we have a sample. Population means that we have everything. The EPA report needs to indicate this error.
    - The biggest issue that may have occurred but was not reported was the use of randomization in the study. There was a good opportunity for the study to be a randomized control trial. Each participant had 1 of 2 treatments tested on one arm and the control on the other arm. There was no indication of randomization used to decide which treatment a participant was provided. For example, left-handed people and right-handed people could be biasing factors to impact different reactions. Because only 3-4 individuals reacted with skin sensitization, it might not have made a difference if randomization was used.
    - Overall, the EPA statement concluded that the study is appropriate for quantitative use for evidence determination, and I agree with that statement.

There were no further comments or questions for the science and statistical discussants.

- **Jennifer Cavallari:** I would like to formulate a response to the Science Review Charge to the HSRB board, "Is the research described in the unpublished study "BIT: Repeated insult patch test, Laboratory final report number 90RC-181" scientifically sound, providing reliable data?". Given the discussion here today, I would like to suggest the following response: "The HSRB concludes that the research described in the unpublished study "BIT: Repeated insult patch test, Laboratory final report number 90RC-181" provides scientifically reliable data." Before voting on this, I would like to open the floor to the board members for any suggestions or edits to this response.
    - **Thomas Lewandowski:** Do we want to specify that the study provided scientifically reliable data for assessing skin sensitization? It is already mentioned in the patch test study part.
    - **Jennifer Cavallari:** I don't know if we usually get that specific. Does EPA have any suggestions on that?
    - **Thomas Lewandowski:** The only reason that I raise this suggestion is because EPA's statistical analysis was aimed at looking at irritation, which then was found to be not useful. I wasn't quite sure whether we wanted to be more specific, but I don't feel strongly about it.
- **Jennifer Cavallari:** The edited charge response now reads: "The HSRB concludes that the research described in the unpublished study "BIT: Repeated insult patch test, Laboratory final report number 90RC-181" provides scientifically reliable data for assessing skin sensitization." Any comments on this new charge?

No further comments were made regarding the updated response. The board unanimously agreed in favor of the response.

- **Michelle Arling:** As a note, we will probably use this study's data in an overall risk assessment to inform point-of-departure in the specific area, but additionally reference it in a larger risk assessment.
    - **Jennifer Cavallari:** Yes, I was concerned about adding skin sensitization with the charge response Dr. Lewandowski recommended. Does it make much of a difference if we add that on or not?
    - **Michelle Arling:** I do not think it does, but I wanted to give a sense of how this will fit in the overall picture.
    - T**homas Lewandowski:** I understand that this is a part of a broader assessment of the chemical. For clarity, will this data not be used for discussing developmental toxicity or other topics?
    - **Michelle Arling:** Yes, that is correct. It will not be used in such discussions in that context.

Dr. Phillip Day led the ethics discussion.

- **Phillip Day:** Thank you to Jennifer and Michelle for their review. I have reviewed the provided study documents concerning the ethical conduct of this study, including the protocol, appendices, and EPA reviews of the scientific and ethical components of the study.
    - I agree with the EPA ethics review and have comments for each relevant section. Subject selection and recruitment, based on the available information, was equitable. Of the 121 enrolled subjects, 10 withdrew from the study prior to research activities.
    - The only inclusion criteria provided was for participants to be aged at least 16 years or

older. In the study, no one under the age of 18 participated. The enumerated exclusion criteria are thorough and were seen on Michelle's slides earlier in the meeting. The criteria are relevant to subject protection.

- Per the memo supplied by the EPA, the principal investigator recounted that subject protection was standard. It was practice at the time to exclude pregnant and breastfeeding women. Any female participant was withdrawn from the study if they became pregnant. However, in reviewing the study documents, no one withdrew from the study for this reason.
- Participation was incentivized, the specific amount is not included in the provided documents. I do not think that is important for the informed consent process. Written informed consent was obtained from all study subjects. However, the means of recruitment and full-consenting process were not provided in the included documents, so I cannot say anything more about that.
- The risks to subjects were adequately minimized, where only three participants experienced a reaction. All three reactions were consistent with expected forms of irritation as outlined in the protocol and consent form.
- Adopting rules for subject monitoring, as described in the study protocol, also served to minimize risks of harm to participants.
- There were seven deviations from the approved protocol that I consider minor deviations because they do not increase the risk of harm for participants and were all recorded appropriately. The deviations included the incidents of three test subjects losing a total of four samples. On three occasions the patch was left on longer than required by the study, and one test subject had results scored late due to a family emergency.
- No major deviations or adverse events were observed or reported during the study.
- Informed consent document adequately discussed study risks and outlines no direct benefit to participants.
- In the event of study related illness, discomfort, or injury, the company would pay for and provide medical care to participants as outlined in the memo supplied to the HRSB and the EPA.
- There was no information provided regarding an independent review. However, Dr. Rimes did recount that these studies would have been subject to an independent review of an ethics board sponsored by Hilltop Research at the time.

Summary: Based on the provided materials and study protocol, it appears that this study was conducted ethically and according to Human Subject Research Regulations. At the time, participants provided written consent, risks were adequately minimized via study design, study procedures were in place to monitor adverse events, and no procedures impaired informed consent. There is no evidence that pregnant or nursing women were enrolled in the study, and while sixteen to seventeen year-olds were eligible, none were enrolled or consented. They also provided a consent form for minors that were not used. The voluntariness of participation was reinforced to participants, and they were informed that they could quit the study at any time.

The charge question reads: "Does available information support a determination that there is no clear and convincing evidence that the conduct of the research was fundamentally unethical or deficient relative to the ethical standards prevailing at the time the research was conducted in a way that place participants at increased risk of harm or impaired their informed consent?" My response is yes, and I would say the information provided supports

the determination.

There were no further comments or questions for the ethics discussants.

- **Jennifer Cavallari:** I would like to formulate a response to the Ethics Review Charge to the HSRB board, "The available information supports the determination that there is no clear and convincing evidence that the conduct of research under review was unethical or deficient relative to ethical standards at the time that the research was conducted." Before voting on this, I would like to open the floor to the board members for any suggestions or edits to this response.
    - **George Milliken:** Regarding the ethical standards in the charge, are the standards something that would not be allowed today?
    - **Phillip Day:** In terms of ethical regulations at the time, they are different now, and there are more standards with greater detail in place when compared to the 1990s. But in general, the current common rule in ethical requirements for human subject research is that ethics are at least consistent with what was in place in the 1990s or following the Declaration of Helsinki. I would defer to Michelle would know more regarding the historical alignment.
    - **George Milliken:** My question was, do we need the final statement to be relative to the ethical standards at the time the research was conducted?
    - **A.J. Allen:** Having looked at Michelle's review and based on my own review, I don't think much has substantially changed. Some parts of how we conduct research now may differ, for example, we would exclude all individuals below 18 years of age and would specifically include or exclude other groups. From the standpoint of the board, we must acknowledge that we cannot retrospectively go back and change how the study was conducted, and this includes the ethics. I think we need a statement regarding the ethical standards at the time because of the issue of second-guessing. Ethical standards will progress over time. There is not anything different in this case, but it must be made clear that at the time the study was conducted, it met all the ethical criteria. If I was on an IRB reviewing this study, I would probably approve it. Some of the study's elements of consent are the one thing that differ today based on ethical standards.
    - **Phillip Day:** I agree with what A.J. said and I think the caveat of the time it was conducted is important as we can expect that there would be changes to practices, and in documentation.
- **Jennifer Cavallari:** Thank you all for the questions and clarifications. We can now vote to respond to the charge as it was originally written, "The available information supports the determination …"

No comments were made regarding the response. The board unanimously agreed in favor of the response.

Dr. Cavallari thanked the board for their time and votes. She will draft a response report of the work done in the meeting and ask the primary discussants to look and review that document once completed. Dr. Cavallari reminded the board this was her and several members' final HSRB board meeting. She informed members in the call that while she will work on the report, the finalization of the report will be completed by Dr. Lisa Corey and Dr. Julia Sharp, and all future meeting report work will be handled by them.

Mr. Tracy reminded the call that the next meeting will take place on September 14th from 2:00 p.m. - 4:00 p.m. EST. He noted the Zoom information will be updated to ensure the next meeting does not

have any technical issues and apologized for the delayed start time of the meeting. Mr. Tracy thanked Dr. Cavallari and Dr. Britt for their service and wished them the best. Dr. Milliken asked Mr. Tracy to repeat the date and time of the next meeting. Mr. Tracy repeated the information and informed that he will send out an invite and reminders.

The meeting adjourned at 3:03 p.m., EST.

Attachment A: HSRB Current Committee Membership

Name	Title	Affiliation
Jennifer Cavallari, ScD, CIH, Chair	Associate Professor	Division of Occupational and Environmental Medicine University of Connecticut Storrs, CT
Alesia Ferguson, Ph.D., Vice Chair	Associate Professor	Department of Built Environment North Carolina A&T State University Greensboro, NC
Janice Britt, Ph.D.	Managing Scientist	ToxStrategies Tallahassee, FL
George Milliken, Ph.D.	Statistical Consultant	Milliken Consultants Manhattan, KS
Mark Aulisio, Ph.D.	Professor	Case Western Research University Cleveland, OH
Thomas Lewandowski, Ph.D.	Principal	Gradient Seattle, WA
Julia Sharp, Ph.D.	Associate Professor	Colorado State University Fort Collins, CO
Albert J. Allen, M.D., Ph.D.	Senior Medical Fellow	Eli Lilly Indianapolis, IN
Lisa Corey, Ph.D.	Toxicologist	Intertox, Inc. Seattle, WA
Eun Um, Ed.D.	President and CEO	AMSTAT Consulting San Jose, CA
Philip Day, Ph.D.	Assistant Professor	University of Texas, Southwestern Dallas, TX

Attachment B: Federal Registers Notice Announcing Meetings

ENVIRONMENTAL PROTECTION AGENCY

[FRL-10017-40-ORD]

Human Studies Review Board; Notification of Public Meetings

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice of public meeting.

SUMMARY: The Environmental Protection Agency (EPA), Office of Research and Development (ORD), gives notice of the 2022 public meetings of the Human Studies Review Board (HSRB). The HSRB provides advice, information, and recommendations on issues related to scientific and ethical aspects of third-party human subjects' research that are submitted to the Office of Pesticide Programs (OPP) to be used for regulatory purposes.

DATES: Four three-day virtual public meetings will be held on:

1. January 25-27, 2022;
2. April 26-28, 2022;
3. July 19-21, 2022; and
4. October 25-27, 2022.

Meetings will be held each day from 1 p.m. to 5:00 p.m. Eastern Time. For each meeting, separate subsequent follow-up meetings are planned for the HSRB to finalize reports from the three-day meetings. These meetings will be held from 2 p.m. to 4 p.m. Eastern time on the following dates: March 17, 2022; June 16, 2022; September 14, 2022; and December 14, 2022.

ADDRESSES: These meetings are open to the public and will be conducted entirely virtually and by telephone. For detailed access information and meeting materials please visit the HSRB Website: https://www.epa.gov/osa/human-studies-review-board.

FOR FURTHER INFORMATION CONTACT: Any member of the public who wishes to receive further information should contact the HSRB Designated Federal Official (DFO), Tom Tracy, via phone/voicemail at: 919-541-4334; or via email at: tracy.tom@epa.gov.

SUPPLEMENTARY INFORMATION:

Background

The HSRB is a Federal advisory committee operating in accordance with the Federal Advisory Committee Act 5 U.S.C. App.2 section 9. The HSRB provides advice, information, and recommendations on issues related to scientific and ethical aspects of third-party human subjects research that are submitted to the Office of Pesticide Programs (OPP) to be used for regulatory purposes.

Meeting access: These meetings will be open to the public. The full agenda with access information and meeting materials will be available seven calendar days prior to the start of each meeting at the HSRB Website: https://www.epa.gov/osa/human-studies-review-board.

For questions on document availability, or if you do not have access to the Internet, consult with the DFO, Tom Tracy, listed under **FOR FURTHER INFORMATION CONTACT.**

Special Accommodations. For information on access or services for individuals with disabilities, or to request accommodation of a disability, please contact the DFO listed under **FOR FURTHER INFORMATION CONTACT** at least 10 days prior to each meeting to give EPA as much time as possible to process your request.

How May I Participate in this Meeting?

The HSRB encourages the public's input. You may participate in these meetings by following the instructions in this section.

1. Oral comments. To pre-register to make oral comments, please contact the DFO, Tom Tracy, listed under **FOR FURTHER INFORMATION CONTACT**. Requests to present oral comments during the meetings will be accepted up to Noon Eastern Time, seven calendar days prior to each meeting date. To the extent that time permits, interested persons who have not pre-registered may be permitted by the HSRB Chair to present oral comments during the meetings at the designated time on the agenda. Oral comments before the HSRB are generally limited to five minutes per individual or organization. If additional time is available, further public comments may be possible.

2. Written comments. For the Board to have the best opportunity to review and consider your comments as it deliberates, you should submit your comments prior to the meetings via email by Noon Eastern Time, seven calendar days prior to each meeting date. If you submit comments after these dates, those comments will be provided to the HSRB members, but you should recognize that the HSRB members may not have adequate time to consider your comments prior to their discussion. You should submit your comments to the DFO, Tom Tracy listed under **FOR FURTHER INFORMATION CONTACT**. There is no limit on the length of written comments for consideration by the HSRB.

Topics for discussion. The agenda and meeting materials will be available seven calendar days in advance of each meeting at https://www.epa.gov/osa/human-studies-review-board.

Meeting minutes and final reports. Minutes of these meetings, summarizing the topics discussed and recommendations made by the HSRB, will be released within 90 calendar days of each meeting. These minutes will be available at https://www.epa.gov/osa/human-studies-review-board. In addition, information regarding the HSRB's Final Reports, will be found at https://www.epa.gov/osa/human-studies-review-board or can be requested from Tom Tracy listed under **FOR FURTHER INFORMATION CONTACT**.

Dated:

Mary Ross, Director, Office of Science Advisor, Policy and Engagement.