EPA-HSRB-22-2

H. Christopher Frey, Ph.D.

Assistant Administrator

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1200 Pennsylvania Avenue, NW

Washington, DC 20460

Subject: July 21, 2022, EPA Human Studies Review Board Meeting Report

Dear Dr. Frey,

The United States Environmental Protection Agency (EPA) requested that the Human Studies Review Board (HSRB) provide a scientific and ethics review of a research study involving human participants. On July 21, 2022, the HSRB considered the unpublished study: "Ladics, Gregory S. BIT: Repeated insult patch test, Laboratory final report number 90RC-181.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". Briefly, the goal of the completed study was to evaluate whether Proxel GXL (1,2-Benzisothiazolin-e-one; BIT) caused irritation or induced contact sensitization to human subjects at concentrations of 500 ppm and 1,000 ppm in a repeat insult patch test. EPA proposes using the quantitative results of this study in risk assessment in a weight-of-evidence determination for the dermal sensitization elicitation threshold to BIT.

The HSRB's responses to the charge questions presented at the meeting on July 21, 2022, along with the rationale for their conclusions and additional considerations and recommendations are provided in the enclosed final meeting report.

Signed,

Lisa Corey, Ph.D.
Co-Chair, HSRB, Acting

Julia Sharp. Ph.D.
Co-Chair, HSRB, Acting

Chair, EPA Human Studies Review Board

INTRODUCTION

On July 20, 2022, the United States Environmental Protection Agency (EPA or Agency) Human Studies Review Board (HSRB or Board) met to address the scientific and ethical charge questions related to an unpublished study unpublished study "BIT: Repeated insult patch test, Laboratory final report number 90RC-181".

REVIEW PROCESS

The Board conducted a public meeting on July 21, 2022. Advance notice of the meeting was published in the *Federal Register* as "Human Studies Review Board; Notification of a Public Meeting" (EPA, FRL-9328-01-ORD). This Final Report of the meeting describes the HSRB's discussion, rationale, recommendations, and consensus in response to the charge questions on ethical and scientific aspects of the completed research.

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

For their evaluation and discussion, the Board considered materials presented at the meeting, the final laboratory report, documentation of ethical conduct, the Agency's science and ethics reviews of the study, as well as oral comments from Agency staff and the investigators during the HSRB meeting discussions. A list of documents provided to the HSRB is available at https://www.epa.gov/osa/july-21-2022-hsrb-meeting.

BIT: Repeated insult patch test, Laboratory final report number 90RC-181

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?

HSRB 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 for assessing skin sensitization.

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

Science review

This study was submitted by DuPont Nutrition and Biosciences to support the dermal sensitization risk assessment of 1,2-Benzisothiazolin-3-one (BIT). The purpose of this study was to determine sensitization potential of BIT (Proxel GXL) in human volunteers using a repeat insult patch test.

There were 121 subjects who entered the study and 111 (85 female, 26 male) completed the study. Data were not available on the race or ethnicity of study subjects. The test substance (BIT, Proxel GXL) at 500 or 1000 ppm in Rhoplex AC-64 or Rhoplex AC-64 alone (the vehicle) was applied directly to the test sites on the skin of the upper arm for 24 hours covered with semi-occlusive patches. Induction applications were made three times per week (on Monday, Wednesday, and Friday) for three successive weeks. The nine applications made during these

three weeks were termed Induction Application Nos. 1 through 9, respectively. All induction applications for individual test samples were made to the same site (the site receiving the original sample at Induction Application No. 1) unless reactions become so strong as to make this inadvisable.

Following a two-week rest period, on Monday of the sixth week, a challenge application of the sample for 24 hours was made to each panelist. The challenge was the same dosing used in the induction phase. Challenge consisted of application to a naive site located adjacent to the original application site. Simultaneous application to a pre-exposed site (i.e., the original site used for Induction Application No. 1) was made concurrently with the challenge at a naïve site (page 4 of Appendix I of study report).

Skin reactions to each patch application were scored Monday, Wednesday and Friday, 48 or 72 hours after each induction application (24 or 48 hours after removal of patches) and 48 hours and 96 hours after challenge application (24 and 72 hours after patch removal). The scoring scale ranged from 0 (no evidence of any reaction) to 5 (vesicular/bullous eruption) with some modification for erythema, skin depth affected, and spread. The only scores other than zero were of 1 (reaction readily visible, but mild) and 2 (definitely popular response).

There were three subjects with clinical responses which were characterized as clinical irritation (Grade 1 erythema) and clinical sensitization (papular response). The one subject with a response suggestive of sensitization was given a rechallenge test, but did not react; thus, those results are also consistent with clinical irritation. There was no other evidence of clinical irritation or sensitization.

There were seven deviations from the study protocol, but the study report states that the deviations did not affect quality or outcome.

Following its assessment, EPA concluded:

> Based on the study results and statistical analysis, BIT is not a dermal sensitizer at the doses used in this study. The No Observed Adverse Effect Level (NOAEL) for this study is 55.6 µg/cm2; there was no LOAEL established in this study.
>
> This study is classified as acceptable/non-guideline. It was submitted by the registrant for fulfillment of a guideline and provides information on elicitation thresholds to BIT in humans.

Statistical Review

While the raw data are provided within the laboratory final report (pages 13 -22 of Laboratory report number 90RC-181, no formal statistical analyses were performed within the Laboratory Report. Rather, the conclusions from the laboratory report consisted of listing the adverse effect responses of three subjects.

EPA in its review of the Laboratory report number 90RC-181 provided five statistical analyses including: a summary of the percentages of positive results for each combination of test type and dose; a McNemar test for each dose level to determine if the probabilities of a positive result are the same for induction and challenge tests among subjects who participated in both phases; a Fisher's exact test for each test type that compared the positivity rates for the high (55.6 µg/cm2) and low (27.8 µg/cm2) dose levels; a a Fisher's exact test for each test type including the vehicle only group; and fitting a set of non-linear mixed statistical models for each test type to predict the probability of a positive result as a function of the dose and a random effect for each subject.

Statistical Review Conclusions

The EPA/ICF statistical analyses were appropriate for this data set. Their statistical analyses did not identify any statistically significant results for comparing the three treatments. Table 1 of the EPA report is a display of the reactions by subject to each of the three treatments.

There is no indication that any randomization process was used in the assignment of treatments which prevents this study from formally being considered as a Randomized Clinical Trial. Since there were so few subjects that responded to the treatments, the use of randomization most likely would not have changed those results.

Recommendations:

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

- The HSRB suggests adding additional information from prior studies to provide additional information about the effects of the vehicle substance, Rhoplex AC-64, and how it might interact with the test substance to increase or decrease bioavailability.
- Within the EPA Science Review, the Board suggests additional clarification surrounding the purpose of the statistical analyses including the goals of the analyses, and identification of a threshold for irritation.
- Since no data were available on subject race and ethnicity, the HSRB recommends that the EPA consider a brief statement on the relevancy of sex, age, race, and ethnicity on the endpoints (potential for skin sensitization) and the limitations, if any, of this missing information.
- Within the EPA Science Review (page 14), the HSRB suggests an adjustment of sentence replacing the phrase ‘study population’ with ‘study sample’ and clarifying that ’10 dropped out’. Specifically, ”The present RIPT study utilized a sample of 111 test subjects

(originally 121 with 10 dropping out of the study) to determine if BIT is a dermal sensitizer at two doses."

- EPA notes that the results of this study are useful as part of a weight-of-evidence approach for assessing skin sensitization potential for BIT. This study also supports a NOAEL that can be used as a point of departure. Due to limitations in the study documentation as noted by EPA and the HSRB, the HSRB encourages EPA to continue to stress the use of this study as part of the WOE and not in isolation.

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?

Response: 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.

Ethics review:

Subject Selection and Recruitment

Based on available information, recruitment and subject selection was equitable. Of 121 enrolled subjects, 10 withdrew from the study prior to research activities. The only provided inclusion criterion was more than 16 years of age, though no one under the age of 18 was enrolled in the study. The enumerated exclusion criteria are thorough and relevant to subject protection. Per the memo supplied by the EPA, the PI recounted that it was standard practice to

exclude pregnant and breastfeeding women, and any female participant was withdrawn from the study if they became pregnant. However, no participants withdrew from the study for this reason. Participation was incentivized, but the specific amount is not included in the provided documents.

Informed Consent Process

Written informed consent was obtained from all study subjects, but the means of recruitment and the consenting process were not in the included documents.

Risks and Benefits

Risks to subjects were adequately minimized. Only three participants experienced a reaction, but all three were consistent with expected forms of irritation as outlined in the protocol and consent form. Stopping rules and subject monitoring as described in the protocol also served to minimize the risk of harm to participants. There were 7 deviations from the approved protocol that can all be considered "minor." Three different test subjects lost a total of 4 samples. On three occasions, subjects wore the patch longer than required by the study and one subject's results were scored late due to a family emergency. These deviations do not increase the risk of harm for participants and were all recorded appropriately. No major deviations or adverse events were observed or reported during the study. The informed consent document adequately discusses study risks and outlines no direct benefit to participants. Finally, in the event of the development of study-related illness, discomfort, or injury the company would pay for and provide medical care to participants.

Independent Ethics Review

No information was provided regarding an independent review other than the information provided by the study PI. Dr. Rheins recounted that these studies would have been subject to review by an independent ethics board sponsored by Hill Top Research.

Review Summary

Based on the provided materials and the study protocol, it appears that this study was conducted ethically and according to human subjects research regulations of the time. Participants provided informed 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 16-17 year-olds were eligible, none were enrolled or consented. The voluntariness of participation was reinforced to participants, and they were informed that they could quit the study at any time.