UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C., 20460

OFFICE OF CHEMICAL SAFETY AND
POLLUTION PREVENTION

June 6, 2022

MEMORANDUM

SUBJECT: Ethics Review of Repeated Insult Patch Test with BIT (1988)

FROM: Michelle Arling, Human Studies Ethics Review Officer
Office of the Director
Office of Pesticide Programs

TO: Anita Pease, Director
Antimicrobials Division
Office of Pesticide Programs

REF: 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.

I have reviewed available information concerning the ethical conduct of the study with human subjects referenced above. If the research is determined to be scientifically acceptable, I find no barrier in regulation to the U.S. Environmental Protection Agency's reliance on this research article in actions under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) or §408 of the Federal Food, Drug and Cosmetic Act (FFDCA). The EPA will ask the Human Studies Review Board (HSRB) to comment on this study.

The submission includes two sets of page numbers. The references in this report are based on the page number in the top right corner of the page, formatted as "Page X of Y".

Summary Characteristics of the Research

The study was conducted "to evaluate the test materials [Proxel GXL and Rhoplex GXL] for the induction of contact sensitization by repetitive applications to the skin of human volunteers and to report any irritation observed with the test material" (p. 8 of 42). Proxel GXL is 1,2-Benzisothiazolin-e-one (BIT). Human subjects were recruited to participate in a repeated insult patch test with an induction and challenge phase, with a rechallenge phase if necessary. Subjects were divided into two groups; one group was tested with 500 ppm Proxel GXL diluted in Rhoplex AC-64 vehicle and the other group was tested with 1000 ppm Proxel GXL diluted in

Rhoplex AC-64 vehicle. Both groups were also tested with Rhoplex AC-64 vehicle alone as a negative control. The test procedure involved application of the test substances to the subjects' upper arms. During the induction phase, application was made by technicians on Mondays, Wednesdays, and Fridays for a total of 9 applications. The test substance was applied, allowed to air dry, and semi-occluded by a patch for at least 24 hours. Subjects removed their own patches after at least 24 hours had elapsed and returned for scoring of reactions 48 or 72 hours after each induction application. Reactions were scored Subjects removed their own patches. Induction applications were all made to the same site on the subject. Following the induction phase, there was a break of approximately two weeks (10-15 days) before subjects began the elicitation phase.

The elicitation phase involved a challenge application of the original test substances to the subjects' skin in a new location adjacent to the original patch location (i.e., naïve site) in addition to the area originally exposed during the induction phase (p. 28 of 42). The exposure of two distinct areas was necessary to "provide a basis for an interpretation of contact sensitization" (p. 28 of 42). A positive reaction at the original exposure site was not considered evidence of sensitization without confirmation of similar observations at the naïve site.

Reactions during both phases of the study were graded based on a scale included in the protocol (pp. 30-31 of 42). The researcher scoring the responses was blinded to the identity of the test substances and previous scores. The same researcher was used to evaluate all reaction sites for a group of subjects. Three subjects had skin reactions (erythema, popular response) during the induction and/or challenge period. After evaluation during the challenge or rechallenge phase, all of the reactions were noted to be consistent with clinical irritation. The report indicated that there was "[n]o other evidence of clinical identifiable irritation or sensitization … on the remaining panelists" (p. 12 of 42).

To obtain more information and to confirm that the study underwent an independent ethics review, I contacted the data submitter and attempted to contact the lab that conducted the study. The sponsor made efforts to obtain information about the ethical conduct of this study, which are summarized in Attachment 1 to this memo. Hill Top Laboratories is now part of Cliantha Research. My inquiries to Cliantha Research by email, phone and through the website contact form were unanswered. Through LinkedIn, I located and reached out to the study's principal investigator, Dr. Lawrence Rheins. In a phone conversation on June 1, 2022, Dr. Rheins confirmed that he is no longer associated with Hill Top Laboratories or Cliantha Research and that he does not have access to records of this specific study. In our conversation, Dr. Rheins shared information about how this type of study was conducted generally during the early 1990s. His comments have been included where applicable in the memo.

1. **Value of the Research to Society**: The objective of this study was to evaluate whether BIT used at two diluted concentration induced sensitization in human subjects. Because this study was measuring the sensory irritation potential in humans, non-human test methods could not be used to satisfy this need. BIT is used as a preservative in a variety of settings (paints, cleaning products, industrial settings). EPA is proposing to use the results of this study to support a risk assessment for BIT. The use of data from a human study will allow EPA to refine the risk assessment.

2. **Subject Selection**:

a. ***Demographics.*** A total of 121 individuals enrolled in the study, and 111 subjects completed the study. Of the subjects who completed the study, 85 were female and 26 were male. Subjects ranged in age from 18 to over 60 years old (p. 9 of 42).

b. ***Eligibility Criteria.*** According to the protocol appended to the study report, subjects were excluded for any of the following reasons: "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 the site of patching" (p. 27 of 42). The protocol allowed for the enrollment of subjects 16 or 17 years old with parental consent and concurrent participation (p. 27 of 42). However, no minors were enrolled in the study (p. 9 of 42).

Dr. Rheins indicated that during the period that this study was conducted, the practice of Hill Top Laboratories was to exclude pregnant and nursing women. He explained that during the consent process, it was the laboratory's job to explain this requirement to women. His recollection is that women were told to use birth control for the duration of the study and to inform the study staff immediately if they became pregnant during the study. At this point, the female subject would be removed from the study immediately.

c. ***Recruitment.*** No information on subject recruitment is included in the study report.

3. Risks and Benefits:

a. ***Risks.*** The study report notes that "[d]ata from both animal and human studies indicated a range of 100 to 1,000 ppm of active ingredient for the analytical trials" (p. 7). The substance could cause skin irritation and sensitization, though at unknown levels in humans.

Of the 121 subjects enrolled, three (subjects 46, 66, and 96) experienced responses during the study. Of the subjects, all three subjects showed effects that were consistent with irritation (p. 7 of 42).

Risks were minimized through stopping rules in the protocol, such as moving the test site during the induction phase if a strong reaction was observed and discontinuing application following observation of a third strong reaction during the induction phase (p. 28 of 42). Individuals with health or skin conditions that could be exacerbated by their participation in the study were excluded from participation in the study. Additionally, the data submitter noted that the doses chosen for this study were based on animal data.

b. ***Benefits.*** There were no directs benefits to the subjects participating in the study. Companies developing and marketing products containing BIT could benefit from the marketing of new products based on the results of this study. The findings of this study

were used to evaluate whether specific doses of BIT induce sensitization in human subjects. Accurate data on levels of BIT that can induce skin sensitization can be used to inform risk assessments.

c. ***Risk-Benefit Balance.*** Risks to subjects were effectively minimized within the study design. The potential societal benefits of establishing a dose of BIT that could induce sensitization outweigh the risks associated with the study.

4. **Independent Ethics Review**: According to the study report, the study was conducted according to the to the Study Director's standard protocol. It is included in the submission as pages 25 to 31. The report notes that there were no modifications to the protocol and seven deviations from the protocol (pp. 8-9 of 42). There is no information about independent ethics review of the research in the study report.

According to Dr. Rheins, at the time this study was conducted Hill Top Research had an independent ethics body review all of this type of research (repeated insult patch test skin sensitization). The institutional review board was sponsored by Hill Top Research, but all members were independent of the lab, study sponsors, and researchers.

5. **Informed Consent**: All subjects provided written informed consent prior to participating in the study. The report notes that "[p]rior to entrance into the study, a brief medical history and the written informed consent were obtained from each subject" (p. 9 of 42) The consent form is included in the study report (p. 32-33 of 42). The consent form outlines the test substance, study procedures, risks and benefits, compensation, and right to withdraw.

6. **Respect for Subjects**: The consent form notes that subjects were free to withdraw at any time, for any reason, and without forfeiting benefits to which they were entitled. Subjects withdrawing during the test were compensated for the time. Medical care was available to all subjects at no cost to them and the sponsor secured workers' compensation coverage for participants as well. Subjects were compensated for their participation. No subjects experienced adverse effects outside of what was expected as part of the study's investigation into sensory irritation.

The consent form notes that every effort to protect subjects' confidentiality would be made (p. 32 of 42). Subjects' identities were protected; subjects were identified by number and no subject's identity was revealed in the study report.

Ten subjects withdrew or were withdrawn from the study for various reasons. Two subjects withdrew because their work schedule changed, four withdrew because they missed two induction applications, one withdrew because they lost their job, one was out of town, and two missed the final scoring.

Applicable Standards

Standards Applicable to the Conduct of the Research

The portions of EPA's regulations regarding the conduct of research with human subjects, 40 CFR part 26 subpart A - L, do not apply since the research was initiated prior to the effective date of the rule on April 7, 2006.

Standards Applicable to the Documentation of the Research

This study was submitted to EPA by DDP Specialty Electronic Materials, US 5, Llc, in support of the dermal sensitization risk assessment for BIT. Consequently, the requirements for the submission of information concerning the ethical conduct of completed human research contained in EPA regulations at 40 CFR part 26, subpart M apply.

For any human research data submitted to EPA after the effective date of April 7, 2006 for EPA's Rule for Protection of Human Subjects, under §26.1303, the person who submits the data is required to 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: (a) copies of all of the records relevant to the research specified by Section 26.1115(a) to be prepared and maintained by an IRB; (b) copies of all of the records relevant to the information identified in Section 26.1125(a) through (f); and (c) copies of sample records used to document informed consent as specified by Section 26.1117, but not identifying any subjects of the research. If any of the information listed in paragraphs (a) through (c) was not provided, the study submitter is required to describe their efforts to obtain the information.

Standards Applicable to EPA's Reliance on the Research

The Agency's rule (40 CFR part 26 subpart Q) defines standards for EPA to apply in deciding whether to rely on research—like this study—involving intentional exposure of human subjects. The applicable acceptance standards from 40 CFR part 26 subpart Q are these:

> **§26.1703.** Except as provided in §26.1706, EPA must 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.
>
> **§26.1704(b).** EPA must not rely on data from any research subject to this section if there is clear and convincing evidence that: (1) The conduct of the research was fundamentally unethical (e.g., the research was intended to seriously harm participants or failed to obtain informed consent); or (2) The conduct of the 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 (based on knowledge available at the time the study was conducted) or impaired their informed consent.

The study was conducted in 1990. The prevailing ethical standards in the 1980s include the 1975 Declaration of Helsinki, the Nuremberg Code (1947), and the Belmont Report (1979). The Declaration of Helsinki underwent a number of revisions through 2013. Some of the key principles from the 1975 Declaration of Helsinki are:

1. Research must be scientifically sound and conducted by qualified personnel.
2. There must be a clear purpose and protocol, reviewed and approved by an independent ethics committee.

3. The importance of the study's objective must outweigh the inherent risks to subjects, and measures to minimize risks must be implemented. The interests of science and society should never take precedence over considerations related to the well-being of the subject.

4. Respect the privacy of subjects and confidentiality of their personal information.

5. Participants should give prior, informed, voluntary consent and have the freedom to withdraw from the study.

Some key principles of the Nuremberg code are: participation must be voluntary and the subjects must be informed of the nature, duration, and purpose of the test and hazards reasonably expected; the research must avoid unnecessary physical and mental suffering; the benefits must outweigh risks; and subjects must have freedom to withdraw. Three key principles from the Belmont Report are: respect for persons (e.g., informed consent); beneficence (as in "do no harm" and maximize benefits/minimize risks); and justice (including equitable selection of participants and avoiding the exploitation of vulnerable populations).

The U.S. Department of Health and Human Services (HHS) and the U.S. Food and Drug Administration (FDA) adopted updated regulations for the protection of human subjects in research and clinical investigations in 1981. These regulations covered informed consent of subjects and protections for the rights and welfare of human subjects involved in research subject to these agencies' jurisdictions. While the research submitted did not cite to these standards, it is reasonable to apply the ethical standards of the 1981 amendments to this study as many institutional review boards followed these standards regardless of the research being reviewed. The rule requires review of proposed research and establishes criteria for approval of such research: risks to subjects must be minimized and reasonable in relation to anticipated benefits (to subjects and/or to resulting knowledge), equitable subject selection, documented informed consent from participants, protection of subjects' privacy and confidential data, and additional safeguards to protect vulnerable subjects.

In addition, FIFRA §12(a)(2)(P) was also in place at the time the research was conducted and requires that human subjects of research with pesticides be "fully informed of the nature and purposes of the test and of any physical and mental health consequences which are reasonably foreseeable" from their participation and freely volunteer to participate.

The Office of Pesticide Programs has a long-standing position that, although there may be gaps in the documentation of the ethical conduct of human research, deficient documentation does not itself constitute evidence that the ethical conduct of the study was deficient relative to the standards prevailing when the research was conducted.

Finally, I defer to scientists for a review of the scientific validity of this human research; if any of the research is determined not to have scientific validity, it would not be ethical to rely on it in regulatory actions under FIFRA.

Compliance with Applicable Standards

Attachment 1 documents the data submitter's efforts to obtain information about the ethical conduct of the study, which satisfies the requirements of 40 CFR 26.1303.

All of the subjects in this study were adults. There is no evidence in the report to indicate that any of the female subjects were pregnant or nursing. Dr. Rheins explained the lab's general practice of excluding pregnant women and the manner in which this occurred. Therefore, EPA's reliance on the research is not prohibited by 40 CFR §26.1703.

Based on the consent form and discussion in the study report, subjects provided written informed consent after receiving information about the study, the risks and benefits of their participation, and their ability to withdraw at any time. Only self-reported healthy adults were eligible to enroll, subjects were notified that any medical expenses that occurred as a result of participation in the study would be paid for by the sponsor/lab. The study protocol included stopping rules in the event a subject showed adverse effects, minimizing the risk of sensitization to subjects. Additionally, subjects were monitored on a regular basis throughout the study period. Dr. Rheins indicated that the research was presented to and overseen by an independent institutional review board, and that the doses selected were likely based on animal data. Given this information and the absence of any information suggesting that the research was fundamentally unethical or intended to harm participants, I conclude that reliance on the research is not prohibited by 40 CFR §26.1704(b).

The consent form included in the study report seems to satisfy the requirements of FIFRA §12(a)(2)(P). Subjects received information about the study, potential risks and benefits, and the pesticide involved prior to enrolling in the study. The form made clear that participation was voluntary and subjects could withdraw at any time.

Conclusion

I find no barrier in law or regulation to reliance on this research (MRID 51171302) in EPA actions taken under FIFRA or §408 of FFDCA. I defer to others for a full review of the scientific validity of this study. If it were determined not to have scientific validity, it would also not be ethically acceptable.

cc: Anita Pease
Elizabeth Donovan
Judy Facey
Tim McMahon
Tim Dole

Attachments

Attachment 1: Documentation of efforts to provide the information required under 40 CFR 26.1303