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

OFFICE OF CHEMICAL SAFETY AND
POLLUTION PREVENTION

September 11, 2023

MEMORANDUM

SUBJECT: Ethics Review of Research Fischer et al. Study Report Involving Intentional of Human Subjects to Formaldehyde

FROM: Michelle Arling, Human Studies Ethics Review Officer
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TO: Anita Pease, Director
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REF: Fischer, T; Andersen, K; Bengtsson, U; Frosch, P; Gunnarsson, Y; Kreilgård, B; Menné, T; Shaw, S; Svensson, L; Wilkinson, J. (1995). Clinical Standardization of the TRUE Test™ Formaldehyde Patch. In Exogenous Dermatology: Advances in Skin-Related Allergology, Bioengineering, Pharmacology and Toxicology. Current Problems in Dermatology, Edited by Surber C and Elsner P. Volume 22:24-30. Basel: S Karger, AG. DOI: https://doi.org/10.1159/isbn.978-3-318-03459-2

I have reviewed available information concerning the ethical conduct of the research described in "Clinical Standardization of the TRUE Test™ Formaldehyde Patch". 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 consult with the Human Studies Review Board (HSRB) prior to relying on research.

Summary Characteristics of the Research

This research was carried out to develop a formaldehyde patch test in order to generate a test material that is "standardized in order to obtain reliable and reproducible results" (p. 25). The testing involved both formaldehyde and a carrier compound, succinimide. Subjects were tested with TRUE Test™ patches at varying doses of formaldehyde, control test patches (formaldehyde

1% in water applied in Finn Chambers), traditional patch tests, and a patch test involving only the vehicles used in the TRUE Test™ patches. For each subject, patches were applied at the same time to the subject's upper back, with the placement of the test and control strips randomized; patches remained on for 48 hours. At 72 hours or 96 hours post-application, the subject's skin was evaluated according to the International Contact Dermatitis Research Group ranking scale.

Testing occurred with 5 groups of subjects. Group 1 included nine healthy volunteers (3 female, 6 male) without known skin disease or sensitivity to formaldehyde, tested with TRUE Test™ patches with 0.12, 0.57, and 1.12 mg/cm^2 formaldehyde. Group 2 was a dose-response study in 25 subjects who were had a positive patch test reaction to formaldehyde; they were tested with TRUE Test™ patches (0.02, 0.03, 0.04, 0.08, 0.12, and 0.15 mg/cm^2 formaldehyde) and traditional patch testing (0.015, 0.032, 0.063, 0.13, 0.25, 0.5, and 1.0% formaldehyde). Group 3 testing was conducted with 120 subjects who had contact dermatitis using TRUE Test™ patches (0.01, 0.02, 0.04, 0.08, 0.12, and 0.15 mg/cm^2 formaldehyde) and traditional patch testing (1.0% formaldehyde). Group 4 was a dose-response study in 24 subjects who were had a positive patch test reaction to formaldehyde; they were tested with TRUE Test™ patches (0.15, 0.2, 0.26, and 0.33 mg/cm^2 formaldehyde) and traditional patch testing (0.1, 0.3, and 1.0% formaldehyde). Group 5 testing was conducted with 255 subjects (159 female, 96 male) who had contact dermatitis using TRUE Test™ patches (0.11, 0.19, 0.26, and 0.33 mg/cm^2 formaldehyde), traditional patch testing (1.0% formaldehyde), formaldehyde standard test used at the clinic where the research was conducted, and patch testing using the same amount of the vehicles [polyvidon (PVP) and N-hydroxymethylsuccinimide (HMS)] as used in the TRUE Test™ patches.

To obtain more information and to confirm that the study underwent an independent ethics review, I made several attempts to contact the study authors. At the time of drafting this review, I have not received a response. Since this study was conducted prior to 1995, it is reasonable to believe that no records are available for this research.

1. Value of the Research to Society:

The publication notes that "formaldehyde is [] a difficult allergen to test with, as the optimal test concentration/dose is close to the threshold of irritation" and that the "goal of test patch optimization is to include at least 90% of sensitive patients" (p. 29). The research was carried out to develop a standardized patch test for formaldehyde that could be "standardized in order to obtain reliable and reproducible test results" (p. 25).

Formaldehyde can be used as a preservative and is found in many household products. Exposure can cause sensitivity, sensitization, contact dermatitis, and other adverse effects. Research into a test that can accurately detect a formaldehyde in 90% of sensitive patients would benefit society; the data generated could be used to inform diagnostic testing and to inform decision-making about levels of exposure.

2. Subject Selection:

a. ***Demographics.*** The demographics of the total study population are not presented in the publication. Group 1 included 3 females and 9 males. Group 5 included 159 females and 96 males.

b. ***Inclusion/Exclusion Criteria.*** The publication does not include much discussion about the subject eligibility criteria beyond this "healthy volunteers without known sensitivity to formaldehyde, consecutive patients with contact dermatitis, and patients with previous patch tests to formaldehyde" (p. 26).

c. ***Recruitment.*** Subjects in groups 2, 3, 4, and 5 were patients at the clinic where the research was being conducted. No information about the recruitment process for control subjects was included in the publication.

3. Risks and Benefits:

a. ***Risks and risk minimization.*** Formaldehyde is a skin irritant, and exposure may cause irritation or dermatitis. The research was conducted at dermatology clinics under the supervision of medical professionals. The formaldehyde-sensitive subjects and subjects with contact dermatitis were already patients at the dermatology clinics where research was being conducted. Control subjects were listed as healthy volunteers. The concentrations of formaldehyde tested in this study, up to 1.12 mg/cm^2 is less than the maximum concentration of formaldehyde used in diagnostic patch testing according to the article (2%, or 20,000 ppm). The other test substances included HMS and PVP. The article notes that "the carrier succinimide [HMS] does not give rise to any unwanted side reactions" (p. 25) and that animal studies did not show dermal irritation or allergic reactions.

Based on the test substances and the exposure levels, subjects participating in the study would not face additional risks beyond what they would experience in participating in a patch test to identify allergens.

b. ***Benefits.*** There were no directs benefits to the subjects participating in the study. Establishing an elicitation threshold for formaldehyde-sensitive individuals will benefit society. This information can be used in clinical evaluations and to inform regulatory decision-making.

c. ***Risk-Benefit Balance.*** The potential societal benefits of this research – establishing a reliable method for detecting formaldehyde allergies and sensitivities - outweigh the risks associated with the study.

4. Independent Ethics Review. The publication notes that the study was approved by ethical committees. No information about the specific committees that oversaw the research or documentation of the ethics review is available in the article, from the investigators, or from the ethics committee.

5. Informed Consent. The article notes that all subjects provided informed consent (p. 26).

6. **Respect for Subjects.** Participant confidentiality was maintained during the study and subjects' privacy was not compromised in the report.

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 neither conducted nor supported by EPA, nor was it initiated on or after to the effective date of the amended Rule for the Protection of Human Subjects.

According to the article, this research was conducted between September 1993 and May 1995. Ethical standards in place at the time this research was conducted include the 1989 Declaration of Helsinki. Some of the key principles 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. Research should be conducted by qualified individuals and under the supervision of a qualified medical professional.
4. 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.
5. Precautions should be taken to maintain the privacy of subjects and confidentiality of their personal information.
6. Participants should give prior, informed, voluntary consent and have the freedom to withdraw from the study. The consent process should include information about the aims, methods, anticipated benefits of and the potential hazards and discomforts associated with the study. Steps should be taken to avoid situations where subjects feel pressure to provide consent for any reason, especially when a physician conducting the study is also caring for the patient outside of the research.

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.

Standards Applicable to the Documentation of the Research

This article was identified by the EPA for consideration. 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 do not apply.

Standards Applicable to EPA's Reliance on the Research

Subpart P of the Agency's rule requires that EPA consult with the HSRB on certain research involving intentional exposure of human subjects as part of the EPA's review of completed human research (40 CFR §26.1604).

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 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 clear and convincing evidence that the ethical conduct of the study was deficient relative to the standards prevailing when the research was conducted.

Another potential standard for human research submitted to EPA is FIFRA §12(a)(2)(P). This passage reads:

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

While this research was conducted with formaldehyde, there is no indication that the formaldehyde used was a pesticide product or that the research was undertaken related to formaldehyde's pesticidal uses. Therefore, the provisions of FIFRA §12(a)(2)(P) related to the use of pesticide in tests on human beings did not apply to the conduct of this research.

Compliance with Applicable Standards

EPA has submitted this study for review by the HSRB in conformance with 40 CFR §26.1604.

There is no evidence that any subjects were minors, or that female subjects were pregnant or nursing. Therefore, EPA's reliance on the research is not prohibited by 40 CFR §26.1703.

There is no clear and convincing evidence that the research was fundamentally unethical. All subjects provided informed consent to participate in the study. The formaldehyde doses chosen for the study were in line with the doses used in clinically administered patch testing to identify

allergies to formaldehyde, indicating no intent to seriously harm the participants existed. Based on these findings, I conclude that reliance on the research is not prohibited by 40 CFR §26.1704(b)(1).

The research was designed with a clear purpose and scientific objectives. The subjects in groups 2-5 were patients at dermatology clinics and the testing associated with the research was likely conducted at these same clinics. Based on the authors' affiliations, the research could have been conducted at hospitals or clinics in Sweden, Denmark, Germany, and the United Kingdom, all of which had ethical standards for human research in place at the time the research was conducted. The article notes that each of the studies/groups of research was approved by an ethics committee. The study was designed with a dose that should allow measurable results without causing adverse effects beyond what would occur with the clinical use of the dosage, and subjects were seen by professionals at the clinics to evaluate the skin exposed to the test substances. The risks to subjects were identified and considered, minimized where possible, and reasonable relative to the expected benefits of the research.

The confidentiality of subjects was maintained during the study and in the publication of the article.

The research was conducted about 30 years ago and it is reasonable to expect that the raw data and information about the ethical oversight of the research are no longer available. Most countries in the E.U. require records to be maintained only for 10 years following the research. At the time the research was published, it was not common to include specific information about the recruitment and consent processes in the publication. However, OPP's position is that the absence of information does not indicate ethical deficiencies.

Based on my evaluation of the research article and consideration of the ethical standards in place when this research was conducted, I conclude that there is no clear and convincing evidence that the conduct of the research was not deficient relative to the ethical standards prevailing at the time. Therefore, reliance on this study is not prohibited by 40 CFR §26.1704(b)(2).

Conclusion

I find no barrier in law or regulation to reliance on this research 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.