**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 Flyvholm et al. Article Involving Intentional of Human Subjects to Formaldehyde

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

**TO:** Anita Pease, Director
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**REF:** Flyvholm, MA, Hall, BM, Agner, T, Tiedemann, E, Greenhill, P, Vanderveken, W, Freeberg, FE and T Menné. (1997). Threshold for Occluded Formaldehyde Patch Test in Formaldehyde-Sensitive Patients. Contact Dermatitis. 36: 26-33.

I have reviewed available information concerning the ethical conduct of the research described in "Threshold for occluded formaldehyde patch test in formaldehyde-sensitive patients". 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 involved both formaldehyde-sensitive subjects (n=20) and healthy control subjects (n=20) exposed dermally to formaldehyde-containing substances through occluded patch testing, non-occluded patch testing, and repeated open application tests (ROAT). The occluded and non-occluded patch testing included formaldehyde solutions of 0. 25, 50, 100, 250, 500, 1,000, 5,000 and 10,000 ppm (p. 28). The occluded patch testing also included a formaldehyde/paraben mix from the European standard series, Germall 115™ and rubber from finger cots. Germall 115 ™ is a product preservative and a formaldehyde releaser. The ROAT used a cosmetic product

containing parabens and Germall 115™, among other common cosmetic ingredients. All three test methods were conducted simultaneously on each subject.

For the occluded patch test, research staff applied the test substance to upper back for 2 days using Finn Chambers on Scanpor tape. Non-occluded testing involved the application of the test substance by a researcher to a 1 $cm^2$ square on subject's forearm and allowed to dry. Readings for both the occluded and non-occluded patch testing occurred at 2 days, 3 days, and 6-9 days. The researchers doing the readings were blinded to the substances, and readings were done according to the International Contact Dermatitis Research Group criteria (p. 29).

Application for the ROAT was done by the subjects to themselves. They "were instructed to apply approximately 0.1 ml of the test material by means of the finger cots 2x daily for a maximum period of 1 week" (p. 30). Subjects were scheduled for readings after 1 week unless a positive reaction was observed sooner. The ROAT grading was done according to a scale described in the publication.

In the occluded test, 10 of the test subjects only reacted at the 10,000 ppm level, "9 reacted to 5,000 ppm, 3 reacted to 1,000 ppm, 2 reacted to 500 ppm and 1 reacted to 250 ppm" (p. 26). The article noted that for the test subjects, no reactions were seen in the non-occluded test or the ROAT. No control subject had a positive reaction to any of the testing conducted.

To obtain more information and to confirm that the study underwent an independent ethics review, I attempted to contact several of the study authors. At the time of drafting this review, I have not received a response. One of the authors responded about another study on which they worked which was published in 1998, and indicated that given the age of the study, none of the records associated with the research were available. Since this study was conducted prior to 1998, it is reasonable to believe that no records are available for this research either.

**1. Value of the Research to Society:**

The publication notes that the study's objective "was to investigate the eliciting threshold of formaldehyde concentration in formaldehyde-sensitive individuals (occluded and non-occluded patch test) and the reaction under experimental use conditions (repeated open application test, ROAT) with a leave-on cosmetic product" (p. 27). 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. Those who are sensitive to formaldehyde "may suffer from long-lasting hand eczema" (p. 26). At the time the research was conducted, the concentrations of formaldehyde that resulted in reactions in formaldehyde-sensitive individuals was much lower than the levels permitted in cosmetic products in the European Union (EU) or in cosmetics (p. 27). The publication notes that "there is a lack of eliciting threshold data based on systematic investigations" (p. 27). Research into elicitation threshold levels in formaldehyde sensitive individuals 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.*** Forty participants were included in the study; 20 formaldehyde-sensitive individuals (14 women, 6 men; ages 32-71), and 20 control subjects (12 women, 8 men; ages 22-54) (p. 27).

b. ***Inclusion/Exclusion Criteria.*** For the formaldehyde-sensitive subjects, the eligibility criteria included being seen by the Dermatology Clinic at Gentofte Hospital between September 1993 and May 1995; having a positive patch test to formaldehyde (1% aq.); having negative patch tests to paraben mix, Germall 115™, and rubber (p. 27). Individuals were excluded if they had "dermatitis or other skin diseases at or near the skin sites to be used for testing, and diseases, exposure of use of medication which could be expected to interfere with the testing" (p. 27). Control subjects were "healthy volunteers … with negative patch tests to formaldehyde, parabens, Germall 115™ and rubber cots" (p. 27).

*c.* ***Recruitment.*** Recruitment of the formaldehyde-sensitive patients was done through the Department of Dermatology at Gentofte Hospital from a pool of patients seen between September 1993 and May 1995. Subjects who met the criteria were recruited into the study (p. 27).

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 a dermatology clinic under the supervision of medical professionals. The formaldehyde-sensitive subjects were already patients at the dermatology clinic where research was being conducted. Control subjects had already been confirmed as healthy volunteers with negative patch tests to all of the materials tested in this study. The concentrations of formaldehyde tested in this study, up to 10,000 ppm, are in line with the concentration of formaldehyde used in diagnostic patch testing (1-2%, or 10,000-20,000 ppm) (p. 26). The other test substances included Germall 115™, a cosmetic product containing common ingredients, and the rubber of the cots used to spread the test substance. Germall 115™ is unlikely to cause skin irritation or skin injury according to the products Safety Data Sheet[1] and three individuals were excluded from participation for their sensitivity to this substance. The article did not include any specific information about risks associated with exposure to the cosmetic product or the rubber cots; any risks to subjects should have been minimal.

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 or using common cosmetic products.

[11] Germall 115™ Safety Data Sheet. Issued 01/06.2012. https://safety365.sevron.co.uk/substances/accessSDS/SDS-7011-57236a44302ad5.96878468

*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 – identifying elicitation thresholds in formaldehyde-sensitive individuals - outweigh the risks associated with the study.

4. **Independent Ethics Review.** The publication notes that the study was approved by the Ethical Committee of the Copenhagen Municipality (p. 27). The Scientific Ethical Committee for the Copenhagen Capital Region is currently registered with the Office of Human Research Protections, and a review board at Gentofte Hospital currently holds a federal-wide assurance. No information about the ethics review is available in the article, from the investigators, or from the ethics committee.

5. **Informed Consent.** The article notes that "all patients gave a written consent to participation after having received oral and written information" (p. 27).

6. **Respect for Subjects.** The publication notes that a total of 36 formaldehyde-sensitive individuals were recruited to participate in the study; however, 16 individuals declined to participate. This supports subjects' freedom from coercion to participate and freedom to withdraw.

   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 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.

All subjects in the study were over 18 years old. There is no evidence that any female subjects were pregnant or nursing. Therefore, EPA's reliance on the research is not prohibited by 40 CFR §26.1703.

There is no evidence that the research was fundamentally unethical. All subjects provided informed consent to participate in the study after receiving information about the study orally and in writing. 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. It was conducted at a dermatology clinic at Gentofte Hospital by qualified staff. An independent ethics committee oversaw the research. 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 clinic 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.

Of the formaldehyde-sensitive individuals who were also patients at the clinic where the research was conducted, 16 of these declined to enroll in the study, suggesting that they were free to decline to participate and the absence of coercion to participate. The confidentiality of subjects was maintained during the study and in the publication of the article.

The research was submitted for publication in a respected journal – Contact Dermatitis. The acceptance for publication suggests that the authors affirmed with the submission that the research was conducted in substantial compliance with Declaration of Helsinki. The research was conducted about 30 years ago, and an email from one of the authors indicated that records associated with the research were no longer available. At the time the research was published, it was not common to include specific information about the recruitment and consent processes in the publication.

Based on my evaluation of the research article and consideration of the ethical standards in place when this research was conducted, I conclude 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.