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

OFFICE OF CHEMICAL
SAFETY AND POLLUTION
PREVENTION

September 11, 2023

MEMORANDUM

SUBJECT: Materials for Review by Human Studies Review Board for the October 11-12, 2023 Meeting

TO: Tom Tracy
Designated Federal Official
Human Studies Review Board
Office of Research and Development

FROM: Michelle Arling
Office of the Director
Office of Pesticide Programs

This memorandum identifies the materials that the Environmental Protection Agency's (EPA's) Office of Pesticide Programs is providing for review by the Human Studies Review Board (HSRB or Board) at the virtual meeting scheduled for October 11-12, 2023. During this meeting, EPA will ask the Board to respond to specific science and ethics questions focused on the research identified below.

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.

The purpose of this study was to investigate the eliciting threshold concentration of formaldehyde in formaldehyde-sensitive individuals in occluded and non-occluded patch tests, and to evaluate the relationship to repeated open application test (ROAT) with a product containing a formaldehyde releaser.

A total of 36 formaldehyde-sensitive patients were recruited as subjects for the study. Of the 36 patients recruited, 20 formaldehyde-sensitive individuals agreed to participate (14 women and 6 men; age range 32 - 71 years). The control group consisted of 20 healthy volunteers with negative patch tests to formaldehyde (12 women, 8 men; age range 22-54 years). Occluded and non-occluded patch tests were conducted with formaldehyde solutions in concentrations of 0, 25, 50, 250, 500, 1,000, 5,000 and 10,000 ppm (equivalent to 0, 0.0025%, 0.0050%, 0.025%,

0.050%, 0.1%, 0.5%, and 1%) and ROAT for 1 week with a leave-on cosmetic product containing on average 300 ppm (equivalent to 0.03%) formaldehyde, were carried out simultaneously on each subject.

In the occluded patch test, 19 of the 20 formaldehyde-sensitive subjects reacted to 10,000 ppm formaldehyde, 9 reacted to 5,000 ppm, 3 reacted to 1,000 ppm, 2 reacted to 500 ppm and 1 reacted to 250 ppm. No definite positive reactions for the formaldehyde-sensitive subjects were observed in the non-occluded patch test or in the ROAT, but follicular reactions were observed in 6 and 5 formaldehyde-sensitive subjects in these tests, respectively.

EPA is proposing to rely on the results of this study for endpoint selection and derivation of a point of departure for elicitation of dermal sensitization from dermal exposure.

The charge questions for the HSRB's consideration are provided below:

Charge to the Board - Science:

- Is the research described in the published study *"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"* scientifically sound, providing reliable data for consideration as part of endpoint selection and derivation of a point of departure for elicitation of dermal sensitization from dermal exposure?

Charge to the Board - Ethics:

- Does available information support a determination that the conduct of the research was not fundamentally unethical?
- Does available information support a determination that the research was not deficient relative to the ethical standards prevailing at the time the research was conducted or conducted in a way that placed participants at increased risk of harm or impaired their informed consent?

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

This publication summarizes clinical studies carried out to develop a patch test using formaldehyde – the TRUE Test™ formaldehyde patch. Because formaldehyde is a highly reactive water-soluble gas, the incorporation of formaldehyde into a dry patch test can be challenging. Therefore, the study authors developed the TRUE Test ™ formaldehyde patch, which utilizes the pro-allergen N-hydroxymethylsuccinimide (HMS). Upon exposure to moisture in the skin, HMS in the TRUE Test dermal patch test undergoes hydrolysis to form

formaldehyde and succinate. The study assessed the dose response of the TRUE Test system versus standard formaldehyde in aqueous solution patch tests (Finn Chamber system) in a range of concentrations for formaldehyde-sensitive individuals as well as those with contact dermatitis. The study aim was to correlate results of the TRUE Test with standard patch testing, as well as establish guidance for concentrations for standard allergen testing with the TRUE Test system to detect contact allergy without inducing irritation. Five different groups were utilized to determine levels at which irritation versus sensitivity occur, as well as a comparison of positive reactions to the TRUE Test system compared to aqueous formaldehyde patch tests at a range of test concentrations.

EPA is proposing to rely on the results of this study for endpoint selection and derivation of a point of departure for elicitation of dermal sensitization from dermal exposure.

The charge questions for the HSRB's consideration are provided below:

Charge to the Board - Science:

- Is the research described in the published study *"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*" scientifically sound, providing reliable data for consideration as part of endpoint selection and derivation of a point of departure for elicitation of dermal sensitization from dermal exposure?

Charge to the Board - Ethics:

- Does available information support a determination that the conduct of the research was not fundamentally unethical?
- Does available information support a determination that the research was not deficient relative to the ethical standards prevailing at the time the research was conducted or conducted in a way that placed participants at increased risk of harm or impaired their informed consent?

<u>Flyvholm et al.</u>

1a. Flyvholm publication

1b. Flyvholm science review

1c. Flyvholm ethics review

1d. Statistical review Flyvolm and Fischer (same file as 2d)

<u>Fischer et al.</u>

2a. Fischer publication

2b. Fischer science review
2c. Fischer ethics review
2d. Statistical review Flyvolm and Fischer (same file as 1d)