



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

OFFICE OF CHEMICAL SAFETY AND
POLLUTION PREVENTION

December 19, 2016

MEMORANDUM

SUBJECT: Ethics Review of Research Article by Claus Zachariae et al. on Methylchloroisothiazolinone/Methylisothiazolinone (2006)

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

TO: Steven Weiss, Chief
Risk Assessment Science Support Branch
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REF: Zachariae, Claus., et al. An evaluation of dose/unit area and time as key factors influencing the elicitation capacity of methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) in MCI/MI-allergic patients. *Contact Dermatitis*. Volume 55, 2006. (MRID 50035302)

I have reviewed available information concerning the ethical conduct of the study referenced in the research article "An evaluation of dose/unit area and time as key factors influencing the elicitation capacity of methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) in MCI/MI-allergic patients" by Claus Zachariae et al. 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 study in actions under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) or §408 of the Federal Food, Drug and Cosmetic Act (FFDCA). EPA will ask the Human Studies Review Board (HSRB) to comment on this study.

Summary Characteristics of the Research

In this study, a total of 39 subjects were enrolled in a study involving diagnostic patch testing and a repeated open application test (ROAT) with methylchloroisothiazolinone/methylisothiazolinone (MCI/MI). Twenty-nine subjects enrolled had previously tested positively for an allergy during a patch test with MCI/MI at a concentration of 100 ppm, and 10 healthy subjects served as controls. The test subjects' pre-existing allergy was confirmed prior to participation in the study with a patch test. As a result of the confirmatory

patch test, 4 test subjects did not qualify to participate in the ROAT because they had a “negative or doubtful reaction”, leaving 25 test subjects to participate in the ROAT. (p. 163) All study participants “were instructed to apply two drops of test material twice a day for 4 weeks” to small areas marked on the inner side of either forearm (p. 162). The consisted of two ROATs, each lasting up to four weeks, separated by a four week wash-out period. In the first ROAT, subjects applied a control and a test material containing 0.025 ug/cm² of MCI/MI. In the second ROAT, subjects applied a control and a test material containing 0.094 ug/cm² of MCI/MI. According to the article, “[t]he development of a positive skin response at any time during the ROAT precluded further participation by the patient in the ROAT.” (p. 163).

The study was approved by the local ethics committee. All subjects gave written informed consent before enrollment in the study.

To confirm that the study underwent an independent ethics review, EPA’s Office of Pesticide Programs contacted Dr. Claus Zachariae, an author of the article, and requested copies of the correspondence with and approval from the ethics committees. Dr. Zachariae indicated that he does not have access to the study documentation, but confirmed that it was reviewed and approved by an independent ethics committee prior to implementation. Dr. Zachariae responded to some questions about the ethical conduct of the study. Relevant questions and responses are included in Attachment 1.

1. Value of the Research to Society:

According to the article, “[t]he aim of this study was to investigate, using the repeated open application test (ROAT), two key parameters of exposure – allergen concentration and time – in terms of the elicitation capacity of MCI/MI in MCI/MI sensitized individuals and to explore the interrelationship between these two key factors.” (p. 161) The results were published in *Contact Dermatitis* in 2006. EPA is proposing to use the results of this study, in combination with results from other ROAT studies, to set a human dermal sensitization endpoint/point of departure in its risk assessment for methylisothiazolinone.

2. Subject Selection:

- a. Demographics.** A total of 39 subjects, at least 18 years old, were invited to participate in the study. Twenty-nine test subjects enrolled had previously tested positively for an allergy during a patch test with MCI/MI at a concentration of 100 ppm. Ten healthy persons served as control subjects. The researchers confirmed the presence or absence of MCI/MI allergy in subjects through a patch test prior to initiating the ROAT. Only 25 of the 29 test subjects qualified to participate in the ROAT based on confirmation of the pre-existing allergy through a patch test with MCI/MI at a concentration of 100 ppm.
- b. Pregnancy and Nursing Status.** Women who were pregnant or nursing were excluded from the study, per the article. (p. 162) According to Dr. Zachariae, pregnancy testing was not performed; subjects were asked prior to enrollment in the study whether they were pregnant or nursing.

- c. Inclusion/Exclusion Criteria.* Inclusion criterion for test subjects was experiencing “at least a positive reaction to the standard MCI/MI patch-test concentration of 100 p.p.m. aq.” prior to enrollment. (p. 162) The inclusion criterion for control subjects were no allergy to MCI/MI. According to the article, “pregnant or lactating women and subjects who had a current acute or chronic widespread eczema at any site were excluded from the study.” (p. 162)
- d. Recruitment.* Test subjects were recruited from patients who had been diagnosed previously with an allergy to MCI/MI at the Department of Dermatology at Gentofte Hospital in Copenhagen, Denmark. The allergy was diagnosed by a positive reaction to a patch test with MCI/MI at 100 ppm. The primary investigator, Dr. Zachariae, contacted potential test subjects by phone to invite them to consider participating. Potential test subjects received a written information sheet about the study by mail. Dr. Zachariae also provided information about the study to potential test subjects orally. In addition to the confirmed allergy, other criteria for test subjects included being at least 18 years old and not being pregnant or nursing.

Control subjects were recruited via advertising local to the study location. The advertisement was posted for a period of weeks in Danish. Dr. Zachariae contacted persons interested in serving as control subjects by phone to invite them to consider participating. Potential control subjects received a written information sheet about the study by mail. Dr. Zachariae also provided information about the study to potential control subjects orally. The criteria for control subjects included no reaction to a patch test with MCI/MI at 100 ppm, not having any active eczema, being at least 18 years old, and not being pregnant or nursing.

3. Risks and Benefits:

- a. Risks.* The risks associated with this study were localized eczema at the site of the ROAT and potential development of a contact allergy to MCI/MI as they are potent contact allergens. Risks were minimized through the inclusion and exclusion factors and monitoring the subjects during the study period. According to the article, “[i]n case of any signs of positive reaction in the test area, study participants were instructed to contact the dermatology department for an unscheduled visit and skin evaluation.” (p. 163)
- b. Benefits.* There are no benefits to the subjects. Society will benefit from increased understanding of the levels of MCI/MI that cause allergic reactions.
- c. Risk-Benefit Balance.* The potential societal benefits of increased understanding of the levels of MCI/MI that cause allergic reactions and effects outweighed the small risks associated with the study.

- 4. Independent Ethics Review:** According to the article, the study was reviewed by local ethics committees in Denmark. (p. 162) I contacted the primary investigator to obtain more information about the ethics committee, standards, and review process. Dr. Zachariae confirmed that the study was reviewed by an independent ethics body prior to implementation. Dr. Zachariae could not recall the name of the ethics committee or provide

the materials reviewed by the ethics committee or correspondence between Dr. Zachariae and the committee because the study was conducted over 10 years ago and the records have not been retained.

5. **Informed Consent:** All subjects gave informed consent before participating. According to Dr. Zachariae, the subjects were fully informed about the identity, nature, and function of the test substances, the study procedure, and the purpose of the study. No subjects withdrew from the study.
6. **Respect for Subjects:** According to Dr. Zachariae, subjects did not receive compensation for their participation in the study; their incentive to participate was “helping research.” The subjects’ identities are not revealed in the study report, subjects were seen only by the primary investigator, Dr. Zachariae, and information about subjects’ identities was kept in Dr. Zachariae’s office in a locked drawer.

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 conducted by a person with the intention to submit the results to EPA.

There is no information in the article about the standards under which the study was conducted. The prevailing standards at the time the study was conducted include the Declaration of Helsinki. In addition to the Declaration of Helsinki, the 2002 International Ethical Guidelines for Biomedical Research Involving Human Subjects by the Council for International Organizations of Medical Sciences (CIOMS) is also informative regarding the prevailing ethical standards. In Denmark, the standards in place at the time the study was conducted included “Ministerial Order No 806 of 12 July 2004 on Information and Consent at Inclusion of Trial Subjects in Biomedical Research Projects” (Attachment 2). The key ethical principles in the Declaration of Helsinki and 2002 International Ethical Guidelines for Biomedical Research Involving Human Subjects are respect for persons, beneficence and justice. The Ministerial Order prohibits biomedical research unless informed consent has been obtained, and establishes the elements of informed consent, including that participation is voluntary and subjects are free to withdraw at anytime without negative effects. Potential subjects must receive information on the study orally and in a written document, both presented in a manner the potential subject can understand, prior to giving written consent to participate in the study.

Standards Applicable to the Documentation of the Research

EPA identified this study through a review of the public literature. No person has independently submitted the published article or any results of this research to EPA. 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

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. 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.

FIFRA §12(a)(2)(P) also applied to this research. This provision 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.

EPA will submit this study for review by the Human Studies Review Board (HSRB) in conformance with 40 CFR §26.1604.

Compliance with Applicable Standards

All of the subjects in this study were at least 18 years old. There are no indications that any of the female subjects were pregnant or nursing. The study director asked female participants prior to enrolling them in the study whether they were pregnant or nursing, and excluded potential subjects who were pregnant or nursing. Based on the available information, there is no compelling evidence that this research involved intentional exposure of any pregnant or nursing female subjects or any children. Therefore, I conclude that EPA's reliance on the research is not prohibited by 40 CFR §26.1703.

The subjects provided written informed consent after receiving information in writing and orally about the study and the risks and benefits of their participation. The protocol underwent independent ethics review and approval by an ethics committee in Denmark. According to Dr. Zachariae, "to the best of my recollection, did the [sic] study meet the standards of the declaration of Helsinki." (Attachment 1) The study involved testing substances found in commercially available cosmetic products, the risks and benefits of the study were explained to the participants prior to enrollment, and subjects were monitored during the study and instructed to visit the dermatology center outside of scheduled visits if a suspected reaction to the substances occurred. Based on these facts, 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)(1) or FIFRA §12(a)(2)(P).

Based on my evaluation of the research article and information provided by Dr. Zachariae, I have also concluded that the conduct of the research was not 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. Subjects provided informed consent prior to enrollment and there is no evidence that consent was not given freely or that subjects were not free to withdraw at any time. The study used a test substance found in commercially available cosmetic products and subjects were monitored during the ROAT. Therefore, reliance on this study is not prohibited by 40 CFR §26.1704(b)(2).

Consistent with the principle of respect for persons, the study purpose and potential risks and discomforts were explained to subjects, subjects were instructed to visit the dermatology department for any suspected adverse effects, and all subjects provided written informed consent. Consistent with the principle of beneficence, the selected dose levels were unlikely to pose more than a minimal risk to subjects, subjects with medical conditions that could increase the likelihood of an adverse effect (e.g., active eczema) were excluded, and the research was conducted in a dermatology department clinic associated with a hospital by trained medical personnel.

Finally, there is no clear and convincing evidence to suggest undue influence or lack of fully informed, fully voluntary consent. The test subjects were recruited from among patients who had visited the dermatology department clinic previously and had a positive reaction to a patch test with MCI/MI at 100 ppm; there is no clear and convincing evidence to suggest that these subjects were vulnerable to undue influence by the medical staff or the researchers regarding their decision about whether to participate in the research. Control subjects were recruited through an advertisement and volunteered to participate. The research was reviewed and approved prior to implementation by an independent ethics committee in Denmark.

Based on these facts, I conclude that the study was not deficient relative to the prevailing ethical standards in a way that placed participants at increased risk of harm or impaired their informed consent.

Conclusion

I find no barrier in law or regulation to reliance on this research (MRID 50035302) 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: Steve Knizner
Tim McMahon
Tim Leighton

Attachments

Attachment 1: Questions to and Responses from Dr. Zachariae
Attachment 2: Ministerial Order No 806 of 12 July 2004 on Information and Consent at Inclusion of Trial Subjects in Biomedical Research Projects (Denmark)