



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 Kerem Yazar, et al. on Methylisothiazolinone (2015)

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
Antimicrobials Division
Office of Pesticide Programs

REF: Yazar, K., et al. Methylisothiazolinone in rinse-off products causes allergic contact dermatitis: a repeated open-application study. *British Journal of Dermatology*. Volume 173, Issue 1, May 2015. (MRID 50035301)

I have reviewed available information concerning the ethical conduct of the study referenced in the research article “Methylisothiazolinone in rinse-off products causes allergic contact dermatitis: a repeated open-application study” by Kerem Yazar 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 post-rule study, a total of 38 subjects aged 19-60 conducted repeated self-application of liquid hand soaps containing methylisothiazolinone five times per day for up to 21 days using a repeated open application test (ROAT). The study was conducted in both Sweden (Centre for Occupational and Environmental Medicine, Stockholm County Council, Stockholm) and Denmark (Gentofte Hospital, Copenhagen). Nineteen test subjects participating in the study were allergic to methylisothiazolinone, and 19 control subjects did not have an allergy

methylisothiazolinone. Prior to participation in the study, all subjects underwent patch testing to confirm their patch-test reactivity to methylisothiazolinone.

During the ROAT, the methylisothiazolinone-allergic subjects were randomly assigned to use soaps containing either 100 ppm methylisothiazolinone (10 subjects) or 50 ppm methylisothiazolinone (9 subjects); all control subjects used the soap containing 100 ppm methylisothiazolinone. All subjects also applied a liquid hand soap not containing methylisothiazolinone as a negative control. Subjects received instructions to apply each soap to the designated area five times per day, and received reminders by text message.

The study lasted approximately 25 days. The patch test was started. After four days, subjects returned to the clinic for a reading of the patch test area. If the results were consistent with the subject's classification in the study (i.e., positive reading for a test subject, negative reading for a control subject), the ROAT began on that day. Readings were taken by a dermatologist each week, around days 11, 18, and 25, and measured from the initiation of the patch test. Subjects were also instructed to visit the clinic sponsoring the study in the event of a skin reaction between scheduled readings. The maximum duration of the ROAT for any subject was 21 days, or three weeks.

Soap containers were provided to subjects on a weekly basis and participants returned the used containers to the clinic. The soap containers were weighed before and after the ROAT to verify the amount used. (p. 117)

The study was approved by regional ethics review boards in Stockholm, Sweden and Capital Region, Denmark. It adhered to the tenets of the Declaration of Helsinki. 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. Carolina Lidén, an author of the article, and requested copies of the correspondence with and approval from the ethics committees. Dr. Lidén provided the following documents (where necessary I used Google Translate to produce a version of the document in English):

- Attachment 1 – Ethical Application – Sweden (Swedish)
- Attachment 2 – Ethical Application – Sweden (English; translated using Google Translate)
- Attachment 3 – Ethical Application – Research Plan (English)
- Attachment 4 – Ethical Approval – Sweden (Swedish)
- Attachment 5 – Ethical Approval – Sweden (English; translated using Google Translate)
- Attachment 6 – Ethical Approval of Amendment – Sweden (Swedish)
- Attachment 7 – Ethical Approval of Amendment – Sweden (English; translated by Dr. Lidén)
- Attachment 8 – Ethical Approval – Denmark (Danish)
- Attachment 9 – Ethical Approval – Denmark (English; translated using Google Translate)
- Attachment 10 – Ethical Approval of Amendment – Denmark (Danish)
- Attachment 11 – Ethical Approval of Amendment – Denmark (English; translated using Google Translate)

EPA also posed questions about the ethical conduct of the study to Dr. Lidén. EPA's questions and Dr. Lidén's responses are included as Attachment 12.

1. Value of the Research to Society:

The objective of this study was investigate if “products preserved with allowed concentrations of methylisothiazolinone (100 ppm) and half that concentration (50 ppm) have the potential to elicit allergic contact dermatitis in previously sensitized individuals.” (p. 116) The results were published in *British Journal of Dermatology* in May 2015. 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 38 subjects participated in the study. Nineteen methylisothiazolinone-allergic subjects aged 19-60 years participated in the study. Nineteen control subjects without an allergy to methylisothiazolinone aged 20-57 also participated in the study. The researchers confirmed the presence or absence of methylisothiazolinone allergy in subjects through a patch test prior to initiating the ROAT.

Two test subjects recruited into the study did not participate in the ROAT phase because they tested negative during the patch test. Another test subject “chose to discontinue the ROAT after 5 days of exposure, before any test reaction on the arms had developed.” (p. 116)

Two control subjects discontinued participation. One control subject voluntarily withdrew from the study after one day. Another was excluded by the study director for not following instructions. (p. 116)

b. Inclusion/Exclusion Criteria. For test subjects, “inclusion criteria were confirmatory patch testing prior to inclusion showing at least one positive reaction to methylisothiazolinone [minimum criteria: erythema and infiltration (+)] and negative patch test to paraben mix. Exclusion criteria were age < 18 years, eczema on the test areas, extensive exposure to ultraviolet light within the last 3 weeks (sunbathing, solarium), systemic immunosuppressive therapy, pregnancy and breastfeeding.” (p. 116).

For control subjects, the “inclusion criteria were confirmatory patch testing prior to inclusion showing no patch-test reactivity to methylisothiazolinone or to paraben mix.” (p. 116) According to the article, the exclusion criteria were the same for control subjects as for test subjects.

c. Pregnancy and Nursing Status. Women who were pregnant or nursing were excluded from the study, as discussed in the article and ethical application. (Attachment 3)

- d. Recruitment.* methylisothiazolinone-allergic subjects were recruited from patients who were had been diagnosed with an allergy to methylisothiazolinone based on a patch test with methylisothiazolinone at 2,000 ppm either at the Centre for Occupational and Environmental Medicine in Stockholm or at the Gentofte Hospital in Copenhagen. See Attachment 1 for a copy of the letter inviting participation from previous patients of the clinics in Swedish and Attachment 2 for an English translation produced using Google Translate. Subjects also met the selection criteria, which included at least one positive reaction to methylisothiazolinone in a patch test, negative patch test to paraben mix, being older than 18 years old, not being pregnant or breastfeeding, not having eczema on the test area, not having extensive exposure to sunlight within 3 weeks of the initiation of the study, and not being on systemic immunosuppressive therapy.

The control subjects were recruited by advertisements posted on two websites. The advertisement was reviewed and approved by the ethics committees, and posted for about 2 months. See Attachment 1 for a copy of the advertisement for control subjects in Swedish and Attachment 2 for an English translation produced using Google Translate. Control subjects also met the selection criteria, which included no patch-test reactivity to methylisothiazolinone or paraben mix, being older than 18 years old, not being pregnant or breastfeeding, not having eczema on the test area, not having extensive exposure to sunlight within 3 weeks of the initiation of the study, and not being on systemic immunosuppressive therapy.

3. Risks and Benefits:

- a. Risks.* The risks and possible side effects are discussed in the informational materials provided to potential test and control subjects. The risks to test subjects were dermatitis/eczema on the ROAT test areas. The risk to control subjects was a small likelihood that they would develop an allergy to methylisothiazolinone. Risks were minimized through the inclusion and exclusion criteria (i.e., not allowing persons with active eczema to enroll in the study), by selecting dose levels that would be unlikely to cause adverse effects (i.e., the concentration approved by the European Union for use in soaps), by limiting the exposure period to three weeks, and by closely monitoring the subjects throughout the study and inviting participants to visit the clinic outside the scheduled monitoring days if an adverse effect developed. If a participant developed an unexpected adverse effect, his or her participation would be stopped. Further, Dr. Lidén noted that the study sponsors provided treatment in the form of a topical corticosteroid at no cost to study participants if the participant developed a strong reaction during the study.
- b. Benefits.* There are no benefits to the subjects. Methylisothiazolinone is a known skin sensitizer and can cause contact allergy in persons who use products containing this ingredient. This study evaluating concentrations of methylisothiazolinone that cause adverse effects in individuals with an allergy to methylisothiazolinone can be used to establish limits and protect both allergic and non-allergic individuals. Further, EPA plans to use these data, in combination with results from other ROAT studies, to set a human dermal sensitization endpoint/point of departure in its risk assessment for methylisothiazolinone.

- c. Risk-Benefit Balance.* The potential societal benefits of increased understanding of the levels of methylisothiazolinone that cause allergic reactions and effects outweigh the small risks associated with the study.
4. **Independent Ethics Review:** The study was reviewed and approved by 2 independent ethics review bodies prior to implementation: regional ethics review boards in Stockholm, Sweden and Capital Region, Denmark. Dr. Lidén provided copies of the correspondence from the ethics committees (see Attachments 4-11). The article notes that “[t]he study adhered to the tenets of the Declaration of Helsinki.” (p.116)
 5. **Informed Consent:** All subjects received information about the study in writing and orally, were offered two opportunities to ask questions [in a telephone conversation with the study directors, Dr. Lidén (Sweden) or Dr. Lundov (Denmark), and at the visit to the clinic, immediately prior to signing the informed consent form and enrolling in the study]. All test and control subjects signed the informed consent form before participating. The information provided to participants explains the research study, the purpose, expected duration of participation, and the procedures to be followed; adequately characterizes the risks and discomforts to subjects; and articulates the right to withdraw from the research at any time.
 6. **Respect for Subjects.** Subjects in Sweden were paid 500 Swedish Krona (~\$54) for participation in the patch test, and 2,500 Swedish Krona (~\$270) for participation in the ROAT (including up to 5 visits to the clinic for instructions). Subjects in Denmark were paid 500 Danish Krone (~\$71) per visit, up to a maximum of 8 visits. The information provided to test and control subjects, as well as the consent form, stated that participation is voluntary and participants could withdraw from the study at any time. Further, in the information provided to test and control subjects, it was noted that subjects’ participation would be discontinued if any unexpected side effects occurred.

Two test subjects recruited into the study did not participate in the ROAT because they tested negative during the patch test. Another test “subject chose to discontinue the ROAT after 5 days of exposure, before any test reaction on the arms had developed.” (p. 116)

Two control subjects discontinued participation. One control subject voluntarily withdrew from the study after one day. Another was excluded by the study director for not following instructions. (p. 116)

The subjects’ identities are not revealed in the article or the materials provided by Dr. Lidén.

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.

The protocol states that the study would be conducted according to the principles in the Declaration of Helsinki. (p. 116) In addition to the Declaration of Helsinki, ethical standards in place at the time the study was conducted included, in Denmark, the Danish “Act on Research Ethics Review of Health Research Projects” (Attachment 13) and “Ministerial Order No 806 of 12 July 2004 on Information and Consent at Inclusion of Trial Subjects in Biomedical Research Projects” (Attachment 14). In Sweden, the ethical standards in place at the time the study was conducted included “The [Swedish] Act concerning the Ethical Review of Research Involving Humans (2003:460)” (Attachment 15).

The key ethical principles in the Declaration of Helsinki are respect for persons, beneficence and justice. The Danish Act establishes requirements for review of research protocols prior to implementation by an independent ethics committee, for providing information to and obtaining informed consent from study participants, and for adequate respect for study participants (e.g., confidentiality of data, adequate compensation, insurance coverage for study-related adverse effects). 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. The Swedish Act seeks to protect individuals’ rights by establishing requirements for research involving human subjects to be reviewed and approved by an ethics committee, outlining the information to be provided to potential subjects, mandating that study sponsors obtain informed consent from subjects prior to enrolling them in the study, and protecting subjects’ personal/confidential information.

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(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.

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

As noted in the article, all of the subjects in this study were over 18 years old. Pregnancy and nursing status were exclusion criteria for test and control subjects. According to Dr. Lidén, female subjects were asked if they were pregnant, could be pregnant, or nursing prior to enrollment in the study. Therefore, it is reasonable to conclude that the research did not involve intentional exposure of any pregnant or nursing female subjects or any children. 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, the risks and benefits of their participation, and their ability to withdraw at any time. The protocol underwent independent ethics review and approval by the Capital Region ethics committee in Denmark and an ethics review body in Stockholm, Sweden. The study involved testing substances found in commercially available soaps and at concentrations at or below the level permitted by the European Union. 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 the information provided by Dr. Lidén, along with Declaration of Helsinki, the Danish Act, Ministerial Order, and the Swedish Act in effect at the time the study was conducted, I 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. The study took adequate precautions to ensure participants' safety by limiting the exposure period, stopping participation in the event of a serious adverse reaction, and using a concentration of the test substance at or below levels approved by the European Union. The informed consent forms in combination with the written information provided to test and control subjects, satisfy the requirements for informed consent under Danish law in place at the time the study was conducted. 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, only subjects with the capacity to understand the

potential risks were allowed to participate, subjects were offered medical care at no cost for study-related injuries, and all subjects provided written informed consent. Consistent with the principle of beneficence, the dose levels were selected based on the levels permitted under European Union standards for soaps and unlikely to pose more than a minimal risk to subjects, subjects with medical conditions that could increase the likelihood of an adverse effect were excluded (i.e., subjects with active eczema outbreaks), and the research was conducted in hospital-based dermatology clinics by trained medical professionals.

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 previous patients at the hospital dermatology clinics who had a confirmed allergy to methylisothiazolinone; there is no clear and convincing evidence to suggest that these subjects were vulnerable to undue influence by the medical staff at the hospitals or the researchers regarding their decision about whether to participate in the research. Test subjects were recruited through advertisements and volunteered to participate. The research was reviewed and approved by the ethics committees in Denmark and Sweden.

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 50035301) in EPA actions taken under FIFRA or §408 of FFDCFA. 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: Ethical Application – Sweden (Swedish)
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- Attachment 12: EPA Questions to and Responses from Dr. Lidén
- Attachment 13: Act on Research Ethics Review of Health Research Projects (Denmark)
- Attachment 14: Ministerial Order No 806 of 12 July 2004 on Information and Consent at Inclusion of Trial Subjects in Biomedical Research Projects (Denmark)
- Attachment 15: The Act concerning the Ethical Review of Research Involving Humans (2003:460) (Sweden)