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

OFFICE OF CHEMICAL SAFETY AND
POLLUTION PREVENTION

May 27, 2021

MEMORANDUM

SUBJECT: Ethics Review of Research Article by Claeson and Lind on Acrolein Eye Irritation Study with Human Subjects (2016)

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

TO: Dana Vogel, Director
Health Effects Division
Office of Pesticide Programs

REF: Anna-Sara Claeson and Nina Lind. Human exposure to acrolein: Time-dependence and individual variation in eye irritation. *Environmental Toxicology and Pharmacology*. Volume 45. pp. 20-27. May 13, 2016. MRID 51570801.

I have reviewed available information concerning the ethical conduct of the study referenced in the research article "Human exposure to acrolein: Time-dependence and individual variation in eye irritation" by Anna-Sara Claeson and Nina Lind 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 ask the Human Studies Review Board (HSRB) to comment on this study.

Summary Characteristics of the Research

The research article summarizes research into the relationship between time of exposure to acrolein and the detection of sensory irritation detection in human subjects. The concentrations of acrolein chosen were "at or below previously reported sensory irritation thresholds that were initially too low to evoke sensory irritation in the eye, but that might do so in exposures of up to 60 min." (p. 21) Subjects participated in four exposure sessions: three different concentrations of acrolein (0.07 mg/m^3, 0.16 mg/m^3, 0.36 mg/m^3), each diluted with heptane to mask the odor, and a fourth of heptane alone (20.3 mg/m^3). The article notes that "[t]he concentrations used at the three exposure times with acrolein were at or below previously reported sensory irritation thresholds (e.g., between 0.13 mg/m^3 and 1.2 mg/m^3" and that "[t]he low and high

concentrations were approximately half the concentration of the Swedish occupational threshold limit for 15 min (0.7mg/m^3) and 8 h (0.2 mg/m^3)". (p. 22) The concentration of heptane used was about 40 times lower than the 8-hour limit value. (Attachment 1) Exposure sessions were 15, 30, 45, and 60 minutes. For each exposure session, a specific amount of the test substance was pumped through a nebulizer, mixed with air, diluted, and pumped into an exposure chamber. To ensure only eye irritation was measured, subjects wore a face mask that covered the nose and mouth. Subjects reported their perceived sensory irritation using a magnitude rating and a level of confidence; this occurred every other minute during the 15-minute exposure period, and every 5 minutes for the other exposure periods, as well as before and aft er each exposure session. Researchers also measured irritation by filming subjects during the exposure to count the number of times the subject blinked at different intervals during the exposure period. Finally, the length of time the subject could keep their eyes open while watching a fixed point on a wall was measured before, immediately after, and 10 minutes following each exposure period.

To obtain more information and to confirm that the study underwent an independent ethics review, EPA's Office of Pesticide Programs contacted Anna-Sara Claeson directly by e-mail. EPA's questions and Ms. Claeson's responses, along with the additional documents provided by Ms. Claeson are included as Attachment 1. This includes the ethics review application in Swedish, the ethics approval letter in Swedish, and the information provided to subjects and the advertisement used, translated by Ms. Claeson. I used Google Translate where necessary to review documents provided in Swedish.

1. **Value of the Research to Society**: The objective of this study was "to examine the time dependence of sensory irritation detection following exposure to threshold levels of the TRPA1 agonist, acrolein, in humans." (p. 21) Because this study was measuring the sensory irritation potential in humans, non-human test methods could not be used to satisfy this need. The article notes that "[s]tudies investigating the effect of time on exposures at or below threshold levels are rare." (p. 21) The research on the sensory irritation of the eyes can be used to inform the "development of guidelines in both occupational and environmental toxicology." (p. 20)

   EPA is proposing to use the results of this study to support a risk assessment for acrolein. The data will be used in a qualitative manner with another more recent study, as the threshold for eye irritation observed in this and the other recent study is similar to the point of departure (POD) EPA plans to use in an acrolein risk assessment.

2. **Subject Selection**:

   a. ***Demographics.*** A total of 26 individuals (18 female, 8 male) were enrolled in the study. Subjects ranged in age from 20 to 47 years old.

   b. ***Eligibility Criteria.*** According to the article and information provided by Ms. Claeson, subjects were eligible if they were between 18 and 60 years old, nonsmokers, not pregnant, and self-reported as healthy.

   c. ***Recruitment.*** Participants were recruited from the area surrounding the test location, using public bulletin boards and the local newspaper. The advertisement provides a

brief overview of the study, some enrollment criteria, the total time for the study, and the compensation (Attachment 1).

3. **Risks and Benefits**:

   a. ***Risks.*** The article notes that "[a]crolein has an acrid, pungent odor, with sensory irritating effects on the mucous membranes, especially in the eyes. It has been shown to exacerbate asthma in children and it is also suspected to contribute to other chronic airway diseases." (p. 21) The risks to subjects were minimized through the exposure levels, research design, and wearing of a protective mask during exposure periods. The levels of acrolein chosen for this experiment were half of the 15-minute and 8-hour exposure limits. The article notes that "[t]he focus of the study was on the detection of sensory irritation, and not to evoke health symptoms." (p. 21) The two subjects who normally wore contact lenses were asked not to wear them during the exposure periods. Additionally, the subjects wore fresh air masks over their noses and mouths to minimize the exposure beyond the eyes.

   b. ***Benefits.*** There were no directs benefits to the subjects participating in the study. The findings of this study may be used to inform risk assessments and acceptable exposure levels of acrolein. EPA will use the results of this study to support an existing point of departure (POD) in the risk assessment of acrolein.

   c. ***Risk-Benefit Balance.*** Risks to subjects were effectively minimized. The potential societal benefits of greater understanding of the sensory irritation from exposure to acrolein outweigh the risks associated with the study.

4. **Independent Ethics Review**: According to the article, the study was reviewed and approved by the Ethics Committee of Umeå University. This is an independent ethics body that operates under the Declaration of Helsinki and the Swedish Ethical Review Act. Attachment 1 shows the approval of the ethics package on May 12, 2012. Ms. Claeson confirmed that the ethics application was reviewed and approved prior to the initiation of the research.

5. **Informed Consent**: All subjects provided informed consent prior to participating in the study. (p. 21) Ms. Claeson noted that consent was obtained through individual meetings between prospective subjects and a study team member. The consent meeting included providing information orally and in writing about the study's purpose, the chemicals that would be used, the risks of participation, and how the study would be conducted. Prospective subjects were also informed that they were permitted to withdraw from the study at any time, for any reason. A summary of the consent topics covered, translated from Swedish to English by Ms. Claeson, can be found in Attachment 1.

6. **Respect for Subjects**: Subjects were compensated for their participation, 100 SEK (~$12) for each visit to the research facility. The total duration of their participation was about 4 hours. An insurance policy covering any injuries that occurred as a result of participation was obtained and the information was shared with the subjects. No subjects experienced adverse effects outside of what was expected as part of the study's investigation into sensory irritation.

Subjects were free to withdraw from participation at any point during the study. Ms. Claeson indicated that no subjects withdrew their participation.

Subjects' identities were protected. All data analysis was performed at the group level, subjects were identified by number, and no subject's identity was revealed in the published article.

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 with the intention to submit the results to EPA.

The article notes that the study was conducted according to the principles in the Declaration of Helsinki (p. 21). In addition to the Declaration of Helsinki, the study was subject to the requirements of the Swedish "Act on Research Ethics Review of Health Research Projects" (Attachment 2). The key ethical principles in the Declaration of Helsinki are respect for persons, beneficence, and justice. The Swedish 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). It also 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 also outlines the responsibilities of the ethics boards and the criteria for reviewing proposed human research.

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.

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 adults. There is no evidence to indicate that any of the 18 female subjects were pregnant or nursing. Pregnancy was an exclusion criteria. Ms. Claeson confirmed that to the best of her knowledge no nursing women were enrolled. 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 Ethics Committee of Umeå University. The study involved testing acrolein and heptane at concentrations at or below the threshold levels set in Sweden. 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).

Based on my evaluation of the research article, the information provided by Ms. Claeson, 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 periods, testing the most sensitive irritation endpoint (eyes), and using a concentration of the test substance at or below levels approved by the European Union. The supplemental materials provided, along with the affirmations from Ms. Claeson, satisfy the requirements for informed consent under Swedish 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, identity of the test substance, and potential risks and discomforts were explained to subjects orally and in writing. Only self-reported healthy adults were eligible to enroll, subjects were notified of insurance

coverage for any incidents that occurred as a result of participation in the study, and all subjects provided written informed consent. Consistent with the principle of beneficence, the selected dose levels were unlikely to result in anything more then temporary irritation of the eyes, minimizing the risk to subjects. Additionally, subjects were monitored closely during and after the exposure sessions.

Finally, there is no clear and convincing evidence to suggest undue influence or lack of fully informed, fully voluntary consent. The subjects received information about the study in writing and orally. Ms. Claeson noted that while students of the university could enroll, none of the study investigators were professors overseeing students. There is no clear and convincing evidence to suggest that any of the subjects were vulnerable to undue influence by the researchers regarding their decision about whether to participate in the research. The study design was reviewed and approved prior to implementation by an independent ethics committee.

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 51570801) 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: Dana Vogel
Donald Wilbur
Shalu Shelat

Attachments

Attachment 1: Responses to EPA Questions on Claeson and Lind Research Article
Attachment 2: Act on Research Ethics Review of Health Research Projects (English translation)