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

OFFICE OF CHEMICAL
SAFETY AND POLLUTION
PREVENTION

July 12, 2021

MEMORANDUM

SUBJECT: Materials for Review by Human Studies Review Board for the July 20-21, 2021 Meeting

TO: Tom O'Farrell
Designated Federal Official Human
Studies Review Board Office of
Science Advisor

FROM: Michelle Arling
Human Research Ethics Review Officer
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 July 20-21, 2021. During this meeting, EPA will ask the Board to respond to specific science and ethics questions focused on the research identified below.

1. **Claeson, A-S and Lind, N. *Human exposure to acrolein: Time-dependence and individual variation in eye irritation*. *Environmental Toxicology and Pharmacology*. Volume 45. pp. 20-27. May 13, 2016.**

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 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). 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). Exposure sessions were 15, 30, 45, and 60 minutes. Various self-reported and researcher-evaluated measures of eye irritation were taken. Because this study was measuring the sensory irritation potential in humans, non-human test methods could not be used to satisfy this need.

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 study is similar to the point of departure (POD) EPA plans to use in an acrolein risk assessment.

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

Charge to the Board - Science:

- Is the research described in the published article "Human exposure to acrolein: Time-dependence and individual variation in eye irritation" scientifically sound, providing reliable data?

Charge to the Board - Ethics:

- Does available information support a determination that the study was conducted in substantial compliance with subpart Q of 40 CFR part 26?

2. Dwivedi, A. et al. Acute effects of acrolein in human volunteers during controlled exposure. *Inhalation Toxicology*. Volume 27, Issue 14. pp. 810-821. December 4, 2015.

The research article summarizes research "to estimate the threshold levels for acute irritation of acrolein" (p. 811) using human subjects. Irritation was measured through physical tests and observations (pulmonary function, nasal swelling, blink frequency, inflammatory markers) as well as subjective ratings by the human subjects. The study was conducted in two phases. For the pilot study, 8 individuals (4 female, 4 male) "were exposed to increasing concentrations of acrolein starting with 0.02, 0.02, 0.07, 0.1, 0.2, and 0.3 ppm, in an exposure chamber" (p. 811) in order to determine the levels of acrolein that should be used in the main study (0.05 ppm and 0.1 ppm). Following the pilot phase, the main study involved 18 individuals (9 female, 9 male). Both acrolein and ethyl acetate were used in this phase; the ethyl acetate was used to mask the odor of acrolein. Each subject was exposed in six different scenarios: "clean air (control), 15 ppm ethyl acetate (EA), 0.05 ppm acrolein (ACR), 0.05 ppm ACR and 15 ppm EA (low ACR + EA), 0.1 ppm ACR (high ACR) and 0.1 ppm ACR, and 15 ppm EA (high ACR + EA)" (p. 811). Up to three subjects participated at a time, seated in the exposure chamber with a controlled climate. At least one week lapsed between each exposure session.

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 study is similar to the point of departure (POD) EPA plans to use in an acrolein risk assessment.

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

Charge to the Board - Science:

- Is the research described in the published article "Acute effects of acrolein in human volunteers during controlled exposure" scientifically sound, providing reliable data?

Charge to the Board - Ethics:

- Does available information support a determination that the study was conducted in substantial compliance with subpart Q of 40 CFR part 26?

Overall Charge

- When considered together, do the studies described in Claeson et al. and Dwivedi et al. provide a scientific weight of evidence in support of the existing short-term to intermediate-term inhalation point of departure of 0.09 ppm based on eye irritation in risk assessments?

Documents for Review

The documents provided to the HSRB for review are listed below.

Claeson & Lind

1. Claeson & Lind article
1a. Science Review Claeson 2016_ForHSRB
1b. Claeson Ethics Review
1c. Attachment 1 Responses to EPA Questions on Claeson Research
1d. Attachment 2 Swedish Ethical Review Act 2003 Translated

Dwivedi et al.

2. Dwivedi et al. article
2a. Science Review Dwivedi 2015_ForHSRB
2b. Dwivedi Ethics Review
2c. Attachment 1 Responses to EPA questions on Dwivedi publication
2d. Attachment 2 Ethics Review Application (Swedish)
2e. Attachment 3 Supplemental Materials (Swedish)
2f. Attachment 4 Swedish Ethical Review Act 2003 Translated

EPA statistical analysis Dwivedi and Claeson studies 2021-07-13
SAS files and datasets of Dwivedi 2015 and Claeson 2016 studies