EPA-HSRB-21-3

Dr. Wayne Cascio

Acting Principal Deputy Assistant Administrator for Science

Performing Delegated Duties of Assistant Administrator

1200 Pennsylvania Avenue, NW

Washington, DC 20460

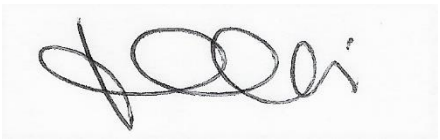
Subject: July 20-21, 2021 EPA Human Studies Review Board Meeting Report

Dear Dr. Cascio,

The United States Environmental Protection Agency (EPA) requested that the Human Studies Review Board (HSRB) provide scientific and ethics review of two research articles involving human participants. On July 20, 2021, the HSRB considered the research article by Dwivedi et al., "Acute effects of acrolein in human volunteers during controlled exposure" (*Inhalation Toxicology*. Volume 27, Issue 14. pp. 810-821. December 4, 2015). On July 21, 2021, the HSRB considered the research article by Claeson and 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). Briefly, the two studies examine the relationship between exposure to acrolein and irritation. EPA is proposing to use the results of these studies qualitatively to support risk assessment for acrolein.

The HSRB's responses to the charge questions presented at the meetings on July 20 and 21, 2021 along with detailed rationale and recommendations for their conclusions are provided in the enclosed final meeting report.

Signed,



Jennifer Cavallari, ScD, CIH

Chair, EPA Human Studies Review Board

INTRODUCTION

On July 20 and 21, 2021, the United States Environmental Protection Agency (EPA or Agency) Human Studies Review Board (HSRB or Board) met to address the scientific and ethical charge questions related to two research articles: Dwivedi et al. "Acute effects of acrolein in human volunteers during controlled exposure." *Inhalation Toxicology*. Volume 27, Issue 14. pp. 810-821. December 4, 2015 and Claeson and 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. EPA is proposing to use the results of these studies qualitatively to support a risk assessment for acrolein. In accordance with 40 CFR part 26, EPA sought HSRB review of the research.

REVIEW PROCESS

The Board conducted a public meeting on July 20 and 21, 2021. Advance notice of the meeting was published in the *Federal Register* as "Human Studies Review Board; Notification of a Public Meeting" (EPA, FRL- 10017-40-ORD). This Final Report of the meeting describes the HSRB's discussion, recommendations, rationale and consensus in response to the charge questions on ethical and scientific aspects of the research.

For each agenda item, the Agency staff presented their review of the scientific and ethical aspects of the research, with each presentation followed by clarifying questions from the Board. The HSRB solicited public comments and next proceeded to address the charge questions under consideration. The Board discussed the science and ethics charge questions and developed a consensus response to each question. For each of the charge questions, the Chair called for the Board to vote to confirm concurrence on a summary statement reflecting the Board's response.

For their evaluation and discussion, the Board considered materials presented at the meeting, research articles, related materials and documents provided by the researchers, the Agency's science and ethics reviews of the research studies, the Agency's statistical analysis of the research data as well as oral comments from Agency staff during the HSRB meeting discussions. A comprehensive list of background documents is available at https://www.epa.gov/osa/july-20-21-2021-meeting-human-studies-review-board.

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.

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?

HSRB Response:

The research described in the published article "Acute effects of acrolein in human volunteers during controlled exposure" is scientifically sound and provides reliable data given the recommendations provided by the HSRB are considered.

The HSRB also has specific comments, recommendations, and additional minor points, which are described in the discussion below.

HSRB detailed response and rationale:

The purpose of this study was to determine the acute irritation threshold for acrolein in humans. The research article included both a pilot study (n=8) and a main study (n=18). Nine male and nine female healthy volunteers were chosen for the main study. Subjects were recruited by advertisement at the Karolinska Institutet. Inclusion criteria were: 20-50 years of age, healthy, non-smoker, no chronic diseases.

In a pilot study to determine the limits of odor and irritation, 4 males and 4 females (who were subsequently participants in the main study) were exposed to increasing levels of acrolein (≥ 99%) at 0.02, 0.04, 0.07, 0.10, 0.20, and 0.30 ppm, in an exposure chamber for 10 minutes at

each level. Volunteers rated symptoms on a 0-100-mm Visual Analog Scale (VAS) on a questionnaire with 10 questions (scale: ‘‘not at all’’ through ‘‘hardly at all’’, ‘‘rather’’, ‘‘quite’’, ‘‘very’’ to ‘‘almost unbearable’’). Based on the results of this pilot study for which no clear effect thresholds could be established, exposure levels for the main study were set at 0.05 and 0.1 ppm for ethical reasons; the highest concentration is the 8-hour occupational exposure level in Sweden.

In the main study, subjects (9 females [average age 23, range 20-26]; 9 males [average age 25, range 21-38]) were exposed on 6 different occasions for 2 hours (at rest) to:

- Clean air
- 15 ppm ethyl acetate (EA)
- 0.05 ppm acrolein (low ACR)
- 0.05 ppm acrolein + 15 ppm EA (low ACR + EA)
- 0.1 ppm acrolein (high ACR)
- 0.1 ppm acrolein + 15 ppm EA (high ACR + EA)

Each session was separated by at least one exposure-free week. Up to three subjects were exposed at the same time in the chamber. The chamber was monitored for acrolein and ethyl acetate concentrations. Ethyl acetate was used to mask the odor of acrolein. Symptoms related to irritation and central nervous system (CNS) effects were rated on a VAS. Symptoms were rated before, during (3, 60, and 118 minutes after start of exposure) and after exposure (20 and 180 minutes and 22 hour). Eye blink (with electromyography, counted in 20-minute intervals, blinded), pulmonary function, nasal swelling (acoustic rhinometry), and various blood and sputum inflammatory markers were also measured.

Based on results of the main study, eye irritation ratings were significantly increased during acrolein exposure with median values of 0 mm, 1.5 mm (close to "not at all"), and 8 mm (a little more than "hardly at all") for control, 0.05 and 0.1 ppm acrolein ($p < 0.001$) at 118 minutes of exposure, respectively, with no influence from co-exposure to ethyl acetate.

Smell ratings increased immediately when subjects entered the chamber and were higher during exposure to ethyl acetate compared to acrolein alone. Median ratings for nose irritation were low (3-4 mm) at four exposure conditions and 6 mm ("hardly at all") at 0.1 ppm acrolein + ethyl acetate. Throat ratings were not affected by acrolein or ethyl acetate. Fatigue ratings were increased at all time points during exposure, with no influence by exposure to acrolein or ethyl acetate. CNS ratings were not affected by acrolein, ethyl acetate, or combined exposure. No gender difference was seen (except for higher rating in females at 60 min of exposure at 0.5 ppm acrolein and day after exposure to 0.1 ppm acrolein + ethyl acetate).

The most sensitive subjects (to eye irritation) had significant association with serum amyloid A after exposure to acrolein (only significant associated found). There were no other associations between symptom ratings and exposure levels.

Blink reflex (recorded by electromyography) was increased the last 20 minutes of exposure at 0.1 ppm acrolein alone compared to the first 20 minutes of exposure ($p=0.049$) but not during the other five exposure conditions. No gender differences were observed.

No significant effects were seen on pulmonary function, nasal swelling, or markers for inflammation and blood coagulation (IL-6, C-reactive protein, serum amyloid A, fibrinogen, factor VIII, von Willebrand factor, and Clara cell protein), or induced sputum (cell count, differential cell count, IL-6 and IL-8).

Authors concluded that based on *subjective* ratings, minor eye irritation was seen with exposure to 0.1 ppm acrolein. They commented that this study had a wider spectrum of objective tests compared with previous studies (e.g., Weber et al., 1976; Weber-Tschopp et al., 1977).

EPA Science Review Findings:

- EPA reviewed this study and found it to be an acceptable, non-guideline study. An Agency guideline study follows those requirements established in the Series 870 Health Effect Test Guidelines and includes factors such as an appropriate dose range, sex distribution, number of test subjects, and parameters to evaluate for a given study type. As this study used human subjects, for which no test guidelines have been established, it was considered to be a non-guideline study but scientifically acceptable for its given purpose.
- EPA noted three deficiencies, none of which change the conclusions or interpretation of the study results.
    - Only two exposure concentrations of acrolein were used in this study (minor for study purposes).
    - Most of the subjects were young (average of 24 years) which may have influenced response to the irritating effects of acrolein (i.e., lower) compared to older individuals which might have a less robust eye tear film (minor).
    - Several deficiencies were identified in the statistical analyses (detailed within the Appendix).

EPA's Statistical Analyses Dated July 13, 2021:

The EPA conducted analyses on the data from Dwivedi et al (2015) study using what are believed to be more appropriate statistical methods. EPA stated their findings in general agreed

with the overall conclusions of the study authors. The only discrepancies between the EPA and original findings were two minor differences:

- It was not clear whether the significant difference between blink frequency during the first and last 20 minutes noted by Dwivedi et al. (2015) was toxicologically significant.
    - EPA stated their re-evaluation showed neither time nor concentration had a significant effect on eye blink frequency. EPA found, "The estimated ratio of eye blink frequency between the 0.1 ppm and 0 ppm acrolein exposure levels was 1.03 (95% CI = 0.97 – 1.09; p-value = 0.384)."
- Also, the significant effect on eye irritation at 120 minutes in the study was present at 60 minutes as well in the EPA analysis. EPA states, "The estimated differences in rankings of eye irritational ratings for exposure to 0.1 ppm and 0 ppm acrolein levels at 60 minutes and 120 minutes after the start of exposure were 0.90 (95% CI = 0.19 – 1.60, p-value = 0.010) and 1.46 (95% CI = 0.76 – 2.15, p-value < 0.001), respectively. The rankings of eye irritational ratings for exposure to 0.1 ppm and 0 ppm acrolein levels were not significantly different at 3 minutes after the start of exposure, 20 minutes post-exposure, 180 minutes post-exposure, and 22 hours post-exposure (all p-values ≥ 0.1)."
    - EPA found neither discrepancy changed the conclusion of the study or impacted the weight of evidence the study has in support of the current inhalation point of departure.

Recommendation

The HSRB agreed with the assessment performed by the EPA and had one additional item for consideration:

- There is limited information on the makeup of the study population that the study was conducted within. A clearer presentation (possibly individual characteristics) of this would be useful to compare to the general US population. It would be valuable to know similarities and differences in the study population as compared to the population who are at risk of exposure with respect to the risk assessment.

Statistical Review

There is mention that the exposure sequences followed a balanced design with up to three subjects were exposed to the same treatment conditions in a chamber. The subjects are the observational units while the group of subjects is the experimental unit. On further examination of the data by EPA, it appears that the exposure condition order was not balanced with uneven subjects at two points during the first exposure and once during the second exposure. Yet, the EPA noted a long wash out period between exposures which would minimize carry-over effects, reducing concern for a balanced design of exposure sequence.

Subjects were in groups of three in a chamber. The experimental (chamber) and observational unit (subject) should be accounted for appropriately in the statistical analysis. EPA could not identify a chamber variable in the data. EPA did not believe that including this variable as a random effect would change the results of the analysis. If this variable is not in the data, then it cannot be included in the analysis and is a limitation of the current analysis. Likewise, treatment order should be considered in the analysis. The randomization scheme was investigated by the EPA and they found that there were some missing observations. However, EPA did not believe that including an order variable would change the results of the analysis they had conducted.

There were multiple outcomes examined in this study, including symptoms ratings (before, during, and post-exposure), blink frequency, airway measurements (before, immediately after, and at 3.5 hours after exposure), nasal swelling (before, immediately after, and at 3.5 hours after exposure), inflammatory and coagulation markers (before, immediately after, and at 3.5 hours after exposure), and inflammatory markers in induced sputum (6 hours from the start of exposure in control and high ACR). Blocking index and markers in blood were log transformed prior to the analyses (motivation for the log transformation is not provided in the published article).

Several statistical analyses were conducted. Friedman's test was used to compare symptoms ratings between exposure levels. Friedman's test is described for the VAS ratings that were not normally distributed. Friedman's test is appropriate for repeated measures with a single factor and could be appropriate here if there is no interaction between EA and ACR. There is no mention of follow-up comparisons between exposure levels if Friedman's test indicated there were differences. Gender differences in symptom ratings were compared using the Mann-Whitney U test. Mann-Whitney U is appropriate for examining differences between groups; however, power will be limited with a small sample size. It is unclear if these tests were conducted at each time point or only one point in time. Inflammatory markers in induced sputum were analyzed using Wilcoxon matched pairs (signed rank) tests. Repeated measures ANOVA was used for all other analyses. Repeated measures ANOVA is appropriate when the variance is considered to be the same across the repeated measures. It is unclear how the assumptions were checked.

A significance level of 0.05 was used for all hypothesis tests. Additional analyses were conducted on the ratings of irritation to compare to quantiles. Logistic quantile regression was used to consider the difference of regression coefficients to 0.25, 0.5, and 0.75 quantiles. It is unclear why this additional analysis was conducted. Cluster bootstrap resampling was used to estimate the sampling error and the correlation between irritation ratings and inflammatory markers in blood. The effect of exposure on the inflammatory markers was expressed as ratios by dividing the value at 3 hours after exposure by the pre-exposure value. The ratios for each level of acrolein were then divided by the ratio computed for the control exposure.

In subsequent analysis of the data by EPA, they appropriately used mixed effects models to analyze the data while accounting for repeated measures over time.

Recommendation

- EPA subsequently conducted linear mixed effects analyses. Because this was a controlled experiment, a follow-up recommendation is to consider a model with fixed main effects and their interactions and not to take out non-significant model terms.

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?

Response:

The Board believes that the research described in the published article "Acute effects of acrolein in human volunteers during controlled exposure" was conducted in substantial compliance with the applicable requirements of 40 CFR part 26.

Ethics review:

Standards Applicable to EPA's Reliance on the Research

40 CFR part 26 subpart Q defines standards for EPA to apply in deciding whether to rely on research involving intentional exposure of human subjects, such as this study.

The applicable standards from 40 CFR part 26 subpart Q are:

> **§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.

The study did not include pregnant persons, and pregnancy was ruled out by testing at the start of the study. While it is not clear whether nursing persons were specifically excluded, there is no indication that any of the participants were nursing. Participants had to be over 18. Therefore, there appears to be no intentional exposure of pregnant or nursing persons, or children.

Informed consent was obtained from all study participants and was appropriately documented. Participants were compensated for their time in study participation, with payment

provided after each study visit so the promise of future payment did not impact ingoing consent. Participants were made aware that they were free to withdraw from the study at any time.

Based on the published paper, and the supplemental materials describing the study conduct in more detail, it appears that all appropriate ethical standards were followed, that the participants were reasonably protected from harms, and there was no information or procedures that impacted voluntary informed consent. The protocol and consent were reviewed and approved by an appropriate local ethical review committee, as per local requirements.

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.

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?

HSRB Response:

The research described in the published article "Human exposure to acrolein: Time dependence and individual variation in eye irritation" is scientifically sound and provides reliable data given the recommendations and concerns provided by the HSRB are considered.

Review

The article looks at the relationship between time of exposure to acrolein and the detection of sensory irritation detection in human subjects across varying concentrations. There were 26 subjects (18 women and 8 men) that each 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 (according to consent form provided by the study author), and a fourth of heptane alone (20.3 mg/m^3). Exposure durations to the three concentrations were 15 minutes (0.36 mg/m^3), 45 minutes (0.16 mg/m^3), and 60 minutes (0.07 mg/m^3) minutes, generally following Haber's equation where concentration x time is a constant. A fourth exposure was 30 minutes to heptane (20.3 mg/m^3) as a control. To measure eye irritation by subjects, a number of

measures were used. Subjects reported eye irritation every minute during the 15-minute exposure session and every 5 minutes during the 45 and 60 minute exposure times, using a scale for level of perceived eye irritation. Blink frequency was measured by videotaping and later counting number of blinks in a given period (2 minutes after beginning exposure, halfway through exposure, and 2 minutes prior to ending exposure) using a hand tally counter; the mean over a 5-minute period was calculated. Tear film break up time (BUT) was self-reported by subjects before, immediately after, and 10 minutes after exposure. Exclusion criteria: failure to self-identify as non-smoking, not pregnant. Subjects self-reported as healthy and completed the Chemical Sensitivity and Perceived Stress Questionnaires.

There was great variability in reported eye irritation from subjects where there was only a slight increase in reported perceived eye irritation. There were 42% that reported no irritation at all. Due to the inter-subject variability, subjects were divided into two groups: responders and non-responders (i.e., those reporting high versus low confidence of perceived exposure), again with perceived intensity increasing over time. In addition, the shortest duration and highest concentration (15 minutes and 0.36 mg/m^3) resulted in significantly more reports of weak to very weak eye irritation right after exposure and 10 minutes after exposure. No significant findings were reported for exposure and blink frequency or exposure and BUT, although differences were found between responders and non-responders (higher for responders in both cases) irrespective of the level of exposure.

EPA Science findings

EPA found minor deficiencies in the study that may or may not affect scientific robustness.

- Heptane control exposure lasted only 30 minutes as opposed to longest 60 minutes for acrolein exposures.
- Twice as many female subjects were included as compared to males subjects, which may create bias in response.
- Measured concentrations of exposure (for quality assurance) were not provided in the chamber.
- The study lacked details on the use of the clean air masks and their efficiency and effectiveness in preventing inhalation exposures and influence on sensitivity and perception.
- Durations between visits were not provided.
- Statistical deficiencies were noted (provided in statistical report).

The HSRB agrees with EPA findings on minor deficiencies, and noted a number of additional deficiencies:

- The details of blink frequency and use of intra-observer or inter-observer methods were not mentioned. For example, having one researcher count blinks and having that count checked by another researcher is a form of inter-observer agreement. This would have provided additional confidence in study results.
- For consistency, the study should have allowed subjects to report eye irritation every minute for all exposure times for reliable comparisons.
- It is unclear whether the decision to analyze responders and non-responders separately was a *post-hoc* decision. A study that restricts analysis to the most sensitive individuals is less informative of effects that may be experienced in the overall population.

- Figure 4 appears to be the heart of the results section and yet interpretation of this figure is challenging.
- The relative humidity (RH) in the study was only 18% and the authors claim such RH are "common in the northern parts of the world." EPA notes that lower humidity could increase irritation potential (due to the eye being dry), but acrolein is water soluble and if there was more moisture in the air, the acrolein may have been more bioavailable to the eye surface.

Recommendations

Due to the uncertainties and methodological limitations indicated above, EPA should only use the Claeson *et al*. study as qualitative support for establishing an exposure limit. In addition, EPA should include a short, high level summary (*i.e*., 1-3 sentences) of some of the limitations and concerns in support of using this study only qualitatively. As noted in EPA's presentation, this study's conclusions do generally support the data obtained from more robust studies, so using the study in a supportive role is reasonable.

- EPA notes that the mean false detection rate among responders was 0.35 whereas that among non-responders was 0.08, a significant difference. The authors present the correct detection (Pc) results in Figure 4, but only after correcting for "false alarms". It would be preferable to present the uncorrected false positive and false negative results for the two groups of subjects. The HSRB suggests that EPA conduct a re-analysis of the eye irritation data along these lines which would also allow for evaluation of potential outliers (*e.g*., if a single subject were influencing the results).

- EPA Data Evaluation Record, Section II A, page 5 of 10. EPA states: "There was a large difference among individuals regarding ratings of eye irritation, as 42% stated no detection at all while 58% rated it as clearly irritating." No subjects rated the exposure as clearly irritating, the graph above this paragraph shows the irritation rating was very weak to weak. EPA should further clarify what is meant by "58% rated it as clearly irritating" to avoid confusion and conflation with respect to the Borg C-100 scale.
- Although there were more females than males, this does allow the findings of the LOAEL (or point of departure) to more possibly remain on the more conservative side. Females tend to be more sensitive to lower concentrations of irritants. Although quoted as a concern by EPA, HRSB recommends that this oversampling of more sensitive population is a reasonable deviation.

Statistical Review

While the subjects in the study consisted of 26 individuals (18 women and 8 men) each subjected to four exposure conditions, after the data were collected, they separated the persons into responders (n=15) and non-responders (n=11). Most all of the conclusions stated in the paper were based on the group of responders.

The authors state "The exposures were executed in a balanced design." In subsequent review and analysis of the data by the EPA, the SAS code provided as an exhibit did not include models with terms to account for the design nor was there any information about the design in the Excel file. The statement does not show the structure of balanced design, and we cannot make any decisions about the analyses without knowing the details of the exposure "balanced" design.

The HSRB noted the following concerns with respect to the statistical analysis.

- Separating persons into two groups (responders and non-responders) post data collection is not a sound statistical practice as it can lead to making more Type I errors, saying there is an effect when there is no effect. The main results in the paper are based on the responders' data (the non-responders' data were excluded). There was far too much variability among the 26 participants (responders and non-responders) to draw any conclusions. Thus, the results and decisions in the paper are based on just the responders' data. This limits the applicability of the results since responders were not selected before data collection. This study provides information that there are a percentage of persons who are responders and a percentage of persons who are non-responders. The information on separation of the persons into responders and non-responders after the data were collected can be used to design a study powered on a specific number of responders.
- There is no indication the model used to analyze the data took into account the possibility of blocking of responders into groups that were tested together in each time period or of the sequence or order effect as participants took part in four sessions. For example, if a person is exposed to the high concentration during the first session, then the person may not be able to notice the effect of the low concentration. Some other persons could detect the low concentration when exposed to the lower concentration before being exposed to a higher concentration. The possibility of a carry-over effect can be likely be controlled by making sure there were sufficient number of days between sessions. There were no indications as to lengths of time between exposures nor as to the order a person was subjected to the exposure conditions. The description of the balanced design used needs to be described in detail, such as balanced for carryover effects, so an appropriate

model can be constructed to describe the data. The authors stated, "*From the regression line a corrected detection threshold at $P_{0.5}$ was calculated for the 15 min exposure condition, C x T = 2.3 (the only condition reaching above chance).This means that acrolein could be detected after 6.8 min of exposure at 0.36 mg/m^3*." This statement seems like no one can detect exposure to 0.36 mg/m^3 of acrolein until 6.8 minutes. The statement should read as 50% of the responders will detect exposure to 0.36 mg/m3 of acrolein by 6.8 minutes. The estimated median time for responders to detect 0.36 mg/m^3 of acrolein was 6.8 minutes. The authors used a simple linear regression model to describe these probabilities, which can produce predicted probabilities is a range of -∞ to +∞. The authors should have used a probability model that keeps the predicted probability between 0 and 1.

- One must be careful in interpretation as the decisions in this study are based on the data of 15 responders. The responder or nor-responder was determined after the data were collected, not a valid statistical process. There is not sufficient information to draw any conclusions about the effect of a person's (either responder or non-responder) exposure to acrolein has on eyes as the analyses presented are for the responders only.

Recommendation

- The HSRB recommends that the EPA consider additional data analyses that considers eye irritation data to explore both the occurrence of outliers and more appropriate modeling techniques, as was done in the reanalysis of the blink and BUT 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?

Response:

The Board believes that the research described in the published article "Human exposure to acrolein: Time-dependence and individual variation in eye irritation." was conducted in substantial compliance with the applicable requirements of 40 CFR part 26.

Review

The applicable standards from 40 CFR part 26 subpart Q are:

> §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.

Subject Selection: Selection of subjects was equitable, and the recruitment procedures were conducted ethically and without apparent coercion. Participants must have been at least 18 years of age to participate. The study did not enroll pregnant individuals and being pregnant was

an exclusion criterion. There was no intentional exposure of any human subject who is a pregnant woman, a nursing woman or her child. (40 CFR part 26 Subpart Q §26.1703)

Informed Consent Process: All subjects provided written informed consent. Participants were provided both written and oral information regarding their eligibility, the purpose of the study, study procedures including risks associated with acrolein, and their ability to end their participation at any time for any reason (or no reason at all). Participation was incentivized. (40 CFR part 26 Subpart Q §26.1704(b))

Risks and Benefits: Risks to subjects were effectively minimized and the overall benefit to society outweighs the possible risks associated with study participation. Participants were also covered by an insurance policy that would cover injuries incurred due to study participation. However, no subjects experienced adverse events or side effects beyond what was expected, and no subjects withdraw from the study. (40 CFR part 26 Subpart Q §26.1704(b))

Independent Ethics Review: The study protocol, consent form, and recruitment materials were reviewed and approved by the Ethics Committee at Umea University (the study site) in accordance with the Declaration of Helsinki. (40 CFR part 26 Subpart Q §26.1704(b))

Based on the published article, the correspondence with Dr. Claeson, and the provided supplemental materials, it appears that the study was conducted according to appropriate ethical standards: an independent ethics review was conducted, subject selection was equitable, risks to subjects were adequately minimized, informed consent was obtained and documented, and no procedures impaired or impacted informed consent.

Charge to the Board – Overall:

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?

Response: When considered together, 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, provided the recommendations and concerns of the HSRB are considered.

Recommendations and concerns

With respect to the weight of the evidence provided by Claeson et al. given the limitations in the study design and data analysis as previously noted, the HSRB recommends that this study should be used for qualitative support only. The two more recent studies presented (Claeson et al. and Dwivedi et al.) found irritation at a higher concentration than the data provided by Weber et al. (0.09 ppm). Therefore, both Claeson et al. and Dwivedi et al provide qualitative support of the point of departure of 0.09 ppm based on Weber et al.