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

OFFICE OF CHEMICAL
SAFETY AND POLLUTION
PREVENTION

April 21, 2023

MEMORANDUM

SUBJECT: Materials for Review by Human Studies Review Board for the May 16-18, 2023 Meeting

TO: Tom Tracy
Designated Federal Official
Human Studies Review Board
Office of Research and Development

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 May 16-18, 2023. During this meeting, EPA will ask the Board to respond to specific science and ethics questions focused on the research identified below.

Mueller, J., Bruckner, T., and Triebig, G. Exposure study to examine the chemosensory effects of formaldehyde on hyposensitive and hypersensitive males. Int Arch Occup Environ Health (2013) 86:107–117. DOI 10.1007/s00420-012-0745-9

The research article summarizes research with 41 adult, male, non-smoking subjects to measure the sensory irritation effects of formaldehyde exposure. Subjects were exposed to formaldehyde on five consecutive days and at five different concentrations (0.0 ppm, 0.3 ppm with 4x15 minute peaks of 0.6 ppm, 0.4 ppm with 4x15 minute peaks of 0.8 ppm, 0.5 ppm, 0.7 ppm) in an exposure chamber. Researchers assessed "objective parameters (conjunctival redness, eye-blinking frequency, tear film break-up time, nasal flow rates) and subjective symptoms" (p. 108). Subjects' nasal sensitivity to irritants was measured using 3 concentrations of carbon dioxide. 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 as part of a weight of evidence determination to establish points of departure for acute inhalation exposure to formaldehyde.

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

Charge to the Board - Science:

- Is the research described in "Exposure study to examine the chemosensory effects of formaldehyde on hyposensitive and hypersensitive males" by Joerg U. Mueller, Thomas Bruckner, and Gerhard Triebig scientifically sound, providing reliable data for use in a weight-of-evidence to determine a point of departure for acute inhalation exposures to formaldehyde?

Charge to the Board - Ethics:

- Does available information support a determination that the conduct of the research was not fundamentally unethical?
- Does available information support a determination that the research was not deficient relative to the ethical standards prevailing at the time the research was conducted or conducted in a way that placed participants at increased risk of harm or impaired their informed consent?

Lang, I., Bruckner, T., and Triebig, G. (2007) Formaldehyde and chemosensory irritation in humans: A controlled human exposure study. Regulatory Toxicology and Pharmacology 50:23-26. DOI:10.1016/j.yrtph.2007.08.012

The research article summarizes research with 21 adult subjects (10 females, 11 males) "to establish possible occurrence of sensory irritation and subjective symptoms in human volunteers exposed to formaldehyde concentrations relevant to occupational exposure" (p. 24). During 10 exposure sessions (2 consecutive Monday-Friday periods), subjects were exposed each day to a different concentration of formaldehyde (0 ppm, 0.15 ppm, 0.3 ppm, 0.3 ppm with peak exposures of 0.6 ppm, 0.5 ppm, and 0.5 ppm with peaks of 1.0 ppm), as well as to formaldehyde (0 ppm, 0.3 ppm, 0.5 ppm, and 0.5 ppm with peaks of 1.0 ppm) and ethyl acetate (12-16 ppm in each exposure period). Objective effects of irritation included "conjunctival redness, blinking frequency, nasal resistance and flow, pulmonary function, and reaction times" (p. 24). 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 as part of a weight of evidence determination to establish points of departure for acute inhalation exposure to formaldehyde.

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

Charge to the Board - Science:

- Is the research described in "Formaldehyde and chemosensory irritation in humans: A controlled human exposure study" by Isabelle Lang, Thomas Bruckner, and Gerhard Triebig scientifically sound, providing reliable data for use in a weight-of-evidence to determine a point of departure for acute inhalation exposures to formaldehyde?

Charge to the Board - Ethics:

- Does available information support a determination that the conduct of the research was not fundamentally unethical?
- Does available information support a determination that the research was not deficient relative to the ethical standards prevailing at the time the research was conducted or conducted in a way that placed participants at increased risk of harm or impaired their informed consent?

Weight of Evidence

The Office of Chemical Safety and Pollution Prevention's (OCSPP) Office of Pesticide Programs (OPP) and Office of Pollution Prevention and Toxics (OPPT) are coordinating a joint hazard characterization for use in their respective human health risk evaluations of formaldehyde. EPA's Integrated Risk Information System Program (IRIS) recently completed a draft Toxicological Review of Formaldehyde – Inhalation (US EPA, 2022a) using information from published literature. Once the National Academy of Sciences, Engineering, and Medicine completes its review of the draft IRIS assessment for formaldehyde, OCSPP plans to rely on the chronic non-cancer inhalation reference concentration (RfC) and cancer inhalation unit risks (IUR) from IRIS. Generally, IRIS does not establish acute or short-term reference concentrations, but due to the anticipated exposures from the Federal Insecticide Fungicide and Rodenticide Act (FIFRA) registered use patterns and Toxic Substances Control Act (TSCA) conditions of use, OCSPP needs to develop acute (24 hours or less) and short-term (1-3 months) inhalation points of departure (PODs), as well as oral and dermal PODs. While IRIS did not derive acute inhalation PODs, they did perform an exhaustive systematic review of the available literature on the toxicity of inhaled formaldehyde which included acute and short-term exposures. OCSPP is using the results of ORD's systematic review supplemented with a second systematic review to look for any studies that may have been published since the last date of the IRIS literature search.

There are a multitude of human studies relevant to acute and short-term exposures to formaldehyde in the published literature. On October 25-26, 2022, the Human Studies Review Board (HSRB) reviewed two studies [Kulle et al. (1987) and Andersen and Mølhave (1983)]. Both studies were found to be scientifically supportable and useful for a weight of evidence approach, with the results from Andersen and Mølhave (1983) useful for qualitative purposes due to a number of limitations including the lack of reporting of key quantitative experimental data, the unclear precision for differentiating between different levels of discomfort between exposure groups, and the inclusion of smokers who may be less sensitive to irritation from inhaled formaldehyde (US EPA, 2022b). For the purposes of the May 2023 meeting of the HSRB, OCSPP is consulting with the HSRB on the scientific and ethical conduct of two

additional human studies with formaldehyde [Lang et al. (2008); Mueller et al. (2013)]. In addition, OCSPP has identified two observational human studies from IRIS [Hanrahan et al. (1984); Liu et al. (1991)] that also will be considered as part of the weight of evidence. OCSPP is soliciting comment from the HSRB on the evaluation of the four intentional exposure human studies reviewed by the HSRB in OCSPP's weight of evidence for acute inhalation endpoints and the proposed PODs.

Table 3. Summary of Proposed PODs

Acute POD Type	Value (ppm)	Value (mg/m^3)	Basis
Peak (15 min)	0.34 ppm	0.42 mg/m^3	Kulle et al. (1987)
8-hr	0.34 ppm[a] (duration-adjusted = 0.13 ppm)	0.42 $mg/m^{3, a}$ (duration-adjusted = 0.16 mg/m^3)	Kulle et al. (1987)
24-hr	0.071 ppm	0.087 mg/m^3	Hanrahan et al. (1984)

a. This value is for a 3-hour exposure. The duration-adjusted value for 8 hours is in parentheses.

Weight of Evidence Charge

- OCSPP has developed a weight of evidence for acute inhalation endpoints for formaldehyde that considered multiple studies and proposed acute inhalation PODs for 3 durations (15-min peak, 8-hr, and 24-hr PODs). Please comment on the use of the 4 studies reviewed by the HSRB (Kulle et al., 1987; Andersen and Mølhave, 1983; Lang et al., 2008; Mueller et al., 2013) in OCSPP's weight of evidence for acute inhalation endpoints and the proposed PODs in Table 3.

Documents for Review

The documents provided for the HSRB are listed below.

Mueller et al.

1a. Mueller article
1b. EPA Science Review – Muller DER
1c. Statistical Report – Lang and Mueller 2-21-23 (same as file 2c)
1d. EPA Ethics Review - Mueller
1e. Online resource 1 SPES
1f. Online resource 2 PANAS
1g. Online resource 3 Conjunctival Redness Both
1h. Online resource 4 Conjunctival Redness Hyposensitive
1i. Online resource 5 Conjunctival Redness Hypersensitive
1j. Online resource 6 Eye Blinking Frequency
1k. Online resource 7 sBUT

1l. Online resource 8 Nasal Flow

1m. Online resource 9 SPES sum score

1n. Online resource 10 SPES eye irritation

1o. Online resource 11 SPES nasal irritation

1p. Online resource 12 SPES olfactory symptoms

1q. Online resource 13 SPES impure air

Lang et al.

2a. Lang article

2b. EPA Science Review – Lang DER

2c. Statistical Report – Lang and Mueller 2-21-23 (same as file 1c)

2d. EPA Ethics Review – Mueller

Weight of Evidence

3a. EPA Weight of Evidence for Acute and Peak Inhalation Endpoints

Additional Reference Documents

4a. October HSRB meeting – Kulle et al. (1987) and Andersen and Mølhave (1983), EPA's reviews, HSRB report: https://www.epa.gov/osa/october-25-27-2022-hsrb-meeting

4b. EPA's Integrated Risk Information System Program (IRIS) - draft *Toxicological Review of Formaldehyde – Inhalation* (April 2022): https://ordspub.epa.gov/ords/eims/eimscomm.getfile?p_download_id=544587

4c. Hanrahan et al. 1984 - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1651796/pdf/amjph00632-0082.pdf

4d. Liu et al. 1991 - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1567965/pdf/envhper00414-0091.pdf