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

OFFICE OF CHEMICAL SAFETY AND
POLLUTION PREVENTION

September 1, 2022

MEMORANDUM

SUBJECT: Ethics Review of Research by Andersen and on Formaldehyde Exposure in Human Subjects (1983)

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

TO: Anita Pease, Director
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REF: Andersen and Mølhave (1983): Chapter 14: Controlled Human Studies with Formaldehyde. In: Formaldehyde Toxicity, James E. Gibson ed. Hemisphere Publishing Group, Washington D.C. Open literature study.

I have reviewed available information concerning the ethical conduct of the study referenced in "A Five-H Exposure Study", in the chapter from Formaldehyde Toxicity titled "Controlled Human Studies with Formaldehyde" by Ib Andersen and Lars Mølhave. 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 was conducted to investigate under controlled conditions the effects of formaldehyde exposure on human subjects over a 5-hour period. The study was conducted at the Institute of Hygiene at Aarhus University, in Århus, Denmark. A total of sixteen subjects enrolled in the study. They were divided into groups of 4 individuals for testing. Each group of four was exposed to four concentrations of formaldehyde (0.3, 0.5, 1.0, and 2.0 mg per cubic

meter of air) in an environmental chamber designed for this type of testing.[1] Prior to the initiation of testing, control measurements were taken from the subjects. Each test day also began with a control period of approximately 2 hours, where the subjects were exposed to clean air in the test chamber. At the 2-hour mark during each test, formaldehyde was added to the chamber and "[a]fter about 1 h a steady state concentration was reached and this was maintained during the rest of the test day" (p. 159). The following measurements occurred three times during the exposure session – during the control, after 2-3 hours of exposure and after 4-5 hours of exposure: nasal mucociliary flow, nasal airflow resistance, forced expiratory vital capacity, and odor threshold for ethyl valerate (p. 159). In addition, subjects reported the degree of airway irritation using a pointer on a voting machine continuously during the testing, and "[a]t the end of each day and the following morning the subjects were questioned as to the degree and nature of discomfort they had experienced" (p. 159). Subjects' performance was measured at various points during the exposure period through tests of numerical addition, multiplication, and card punching.

To obtain more information and to confirm that the study underwent an independent ethics review, I made multiple attempts to contact Dr. Andersen and Dr. Mølhave, as well as the institution where the testing occurred (Aarhus University in Denmark) and the institute where Dr. Mølhave is a Professor Emeritus. I also reached out to the International Society of Indoor Air Quality and Climate, an organization that presented Lifetime Achievement Awards to both of the researchers. None of my requests for information was answered.

1. **Value of the Research to Society**: The publication notes that individuals are exposed to formaldehyde in both occupational settings and residential settings. Residentially, exposure comes from "the widespread use of formaldehyde in building materials such as particleboard, plywood, and insulation materials and in furniture and textiles" (p. 154). This research was conducted to evaluate the effects of exposure to various levels of formaldehyde under controlled conditions. Research existing at the time this study was conducted only measured the effect of exposure in humans for short durations; this study measured the exposure over a longer duration of up to 5 hours. Because this study was measuring the sensory irritation potential in humans, non-human test methods could not be used to satisfy this need. The research on the effects of exposure to formaldehyde and the levels at which measurable effects occur can be used to inform both occupational and environmental toxicology.

2. **Subject Selection**:

   a. ***Demographics.*** A total of 16 individuals (5 female, 11 male) were enrolled in the study. Subjects ranged in age from 20 to 33 years old.

   b. ***Eligibility Criteria.*** The publication notes that none of the subjects had been or were exposed to formaldehyde, all had apparently healthy upper airways, were all nasal breathers, and did not have a history of chronic or recent acute respiratory disease (p. 158).

[1] I. Andersen and G.R. Lundqvist. Design and performance of an environmental chamber. *Int. J. Biometeor.* 14:402-405 (1970).

c. ***Recruitment.*** The publication does not include information about the recruitment of subjects.

3. Risks and Benefits:

a. ***Risks.*** The Centers for Disease Control notes that "At low levels, breathing in formaldehyde can cause eye, nose and throat irritation. At higher levels, formaldehyde exposure can cause skin rashes, shortness of breath, wheezing and changes in lung function. Children, the elderly and people with asthma or other breathing problems may be more sensitive to the effects of formaldehyde."[2] The researchers estimated that "approximately 10% of the population in Denmark [was] exposed to formaldehyde concentrations about 0.15 mg/cubic meter" (p. 154). They also noted that at the time the study was conducted, the "threshold limit value (TLV) for formaldehyde in the United States [was] 3.6 mg/cubic meter" (p. 163). The doses tested in the study were 0.3, 0.5, 1.0 and 2.0 mg formaldehyde per cubic meter, lower than the then-existing US-based TLV for formaldehyde. The risks to subjects were minimized through the setting exposure levels lower than the existing TLV, enrolling subjects who had healthy airways and no history of respiratory disease, and prohibiting smoking during the exposure periods. The subjects' primary complaints immediately following exposure periods were eye irritation and dryness in the nose and throat. However, the morning following each exposure period, subjects did not report any remaining irritation (p. 162).

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 to determine a threshold for sensory irritation from exposure to formaldehyde.

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

4. Independent Ethics Review: The publication does not include any information about independent ethics review of the proposed research or oversight of the study.

5. Informed Consent: The publication does not include any information about obtaining informed consent from the subjects.

6. Respect for Subjects: There is no information in the publication about compensation for subjects. There are no reports of subjects experiencing adverse effects outside of what was expected as part of the study's investigation into sensory irritation.

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.

[2] https://www.atsdr.cdc.gov/formaldehyde/

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.

This research was likely conducted in the 1970s. Prevailing ethical standards in the 1970s include the 1975 Declaration of Helsinki and the Nuremberg Code (1947). Some of the key principles from the 1975 Declaration of Helsinki are:

1. Research must be scientifically sound and conducted by qualified personnel.
2. There must be a clear purpose and protocol, reviewed and approved by an independent ethics committee.
3. The importance of the study's objective must outweigh the inherent risks to subjects, and measures to minimize risks must be implemented. The interests of science and society should never take precedence over considerations related to the well-being of the subject.
4. Respect the privacy of subjects and confidentiality of their personal information.
5. Participants should give prior, informed, voluntary consent and have the freedom to withdraw from the study.

Some key principles of the Nuremberg code are: participation must be voluntary and the subjects must be informed of the nature, duration, and purpose of the test and hazards reasonably expected; the research must avoid unnecessary physical and mental suffering; the benefits must outweigh risks; and subjects must have freedom to withdraw. Three key principles from the Belmont Report are: respect for persons (e.g., informed consent); beneficence (as in "do no harm" and maximize benefits/minimize risks); and justice (including equitable selection of participants and avoiding the exploitation of vulnerable populations).

The Office of Pesticide Programs has a long-standing position that, although there may be gaps in the documentation of the ethical conduct of human research, deficient documentation does not itself constitute evidence that the ethical conduct of the study was deficient relative to the standards prevailing when the research was conducted.

Finally, I defer to scientists for a review of the scientific validity of this human research; if any of the research is determined not to have scientific validity, it would not be ethical to rely on it in regulatory actions under FIFRA.

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 indication in the publication that any of the female subjects were pregnant or nursing. Based on the available information, there is no evidence that the research involved intentional exposure of any pregnant or nursing female subjects. EPA's reliance on the research is not prohibited by 40 CFR §26.1703.

The study design included precautions to ensure participants' safety by enrolling healthy subjects, limiting the exposure periods, testing doses below then-existing threshold limit value, and closely monitoring subjects during the exposure period. Although the publication did not include information about informed consent from subjects or review and oversight by an institutional review board, the lack of information does not necessarily indicate that the conduct of the study was unethical. It was not uncommon for published research in the 1970s and early 1980s to omit any information about the ethical conduct of the study. As noted earlier, it is the position of the Office of Pesticide Programs that deficient documentation does not itself constitute evidence that the ethical conduct of the study was deficient relative to the standards prevailing when the research was conducted.

There is no evidence in the available information that the research was fundamentally unethical or intended to harm participants. Further, there is no evidence that 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. Therefore, I conclude that reliance on the research is not prohibited by 40 CFR §26.1704(b).

Conclusion

I find no barrier in law or regulation to reliance on this research 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: Jeff Dawson
Anna Lowit