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 Articles by Thomas J. Kulle et al. on Formaldehyde Dose-Response in Healthy Non-Smokers (1987, 1993)

FROM: Michelle Arling, Human Studies Ethics Review Officer (Acting)
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TO: Anita Pease, Director
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REF: Kulle, T.J.; Sauder, L.R.; Hebel, J.R.; Green, D.J.; Chatham, M.D. (1987): Formaldehyde Dose-Response in Healthy Non-Smokers. *JAPCA* 37: 919-924. DOI: 10.1080/08940630.1987.10466285

Kulle, T.J. (1993). Acute Odor and Irritation Response in Healthy Nonsmokers with Formaldehyde Exposure. *Inhalation Toxicology* 5(3): 323-332. DOI: 10.3109/08958379308998389

I have reviewed available information concerning the ethical conduct of the single study referenced in the two published articles, "Formaldehyde Dose-Response in Healthy Non-Smokers" and "Acute Odor and Irritation Response in Healthy Nonsmokers with Formaldehyde Exposure". 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 research.

Summary Characteristics of the Research

Two published articles summarize a single study. In this research, 19 subjects were divided into two groups to investigate a dose-response relationship between formaldehyde exposure and irritation under controlled conditions. One group of 10 subjects "were randomly

exposed to HCHO [formaldehyde] concentrations of 0.0, 0.5, 1.0, and 2.0 ppm at rest, and 2.0 ppm with exercise" (Kulle 1987, p. 920). The second group (9 subjects) "were randomly exposed to HCHO concentrations of 0.0, 1.0, 2.0 and 3.0 ppm at rest, and 2.0 ppm with exercise" (Kulle 1987, p. 920). For the exercise exposure period, subjects "performed an 8-min bicycle ergometer exercise… every ½ hour, and minute ventilation was measured between the fourth and fifth minutes of each exercise stint" (Kulle 1987, p. 920). Exposure periods were 180 minutes in an environmentally-controlled chamber at the University of Maryland. Subjects served as their own controls during the study, exposures were separated by 1 week, and subjects were studied at the same time each day.

Various measurements were taken during the study. "Spirometric measurements were performed prior to and during exposure at t = 0, 30, 60, 90, 120, 150, 180 min" for all exposures, and at 24 hours post-exposure for the 3.0 ppm and 2.0 ppm with exercise test periods (Kulle 1987, p. 920). Airway resistance and thoracic gas volume were measured before and after exposure period and again 24 hours after the exposure period. Non-specific airway reactivity was assessed at the end of each exposure period, and at 24 hours post-exposure. Nasal resistance was measured before and following exposure to 2.0 or 3.0 ppm. Finally, all subjects completed symptom questionnaires immediately before and after the exposure periods, as well at 24 hours post-exposure.

Subjects also participated in a methacholine challenge, exposed to methacholine aerosol at doses from 0.31 to 50 mg/mL until reaching a 40 percent reduction in their specific airway conductance. This was to measure their airway activity.

The published article contains little information about the ethical conduct of the study. To obtain more information and to confirm that the study underwent an independent ethics review, I attempted to conduct the study's primary author, Dr. Thomas J. Kulle, as well as all of the other authors on the 1987 publication. Dr. Kulle passed away in 2010. I received no responses to attempts to contact any of the other authors through email, website contact forms, and by phone.

1. Value of the Research to Society:

The 1987 publication notes that "formaldehyde (HCHO) is a ubiquitous organic compound with substantial industrial and indoor (commercial and domestic) sources of exposure" (Kulle 1987, p. 919). Exposure to formaldehyde at varying doses can provide a range of symptoms, including eye and upper respiratory tract irritation, as well as bronchoconstriction. In order to investigate the levels at which specific effects occur, "[t]he purpose of this study was to investigate dose-response relationships for changes in symptoms and pulmonary function associated with acute exposures to 0.0 to 3.0 ppm HCHO [formaldehyde] in an environmental research chamber" (Kulle 1987, p. 919). Due to the lack of scientific investigation into the effects of formaldehyde exposure, the range of settings where it is encountered, and the varying levels present, the data from this study can be used to inform decision-making about levels of exposure in both occupational and residential settings.

2. Subject Selection:

a. ***Demographics.*** A total of nineteen subjects participated in the study, 10 males and 9 females (Kulle 1993, p. 326), with an average age of 26.3 (Kulle 1987, p. 920).

b. ***Inclusion/Exclusion Criteria.*** The subjects in the study were non-smokers, who "denied a history of allergy, asthma, hay fever, or upper respiratory infection in the 6 weeks prior to the study (Kulle 1987, p. 919). Prior to the testing with formaldehyde, "[t]he subjects underwent a screening examination including medical history, physical exam, ECG, pulmonary function tests, and nonspecific airway reactivity by methacholine challenge" (Kulle 1987, p. 919).

c. ***Recruitment.*** The article does not include any information about the recruitment process.

3. Risks and Benefits:

a. ***Risks.*** The article does not describe the risks to study participants specifically. It notes that "[i]rritation of the eyes and upper respiratory tract is the most frequent finding associated with these exposures; bronchoconstriction has been described in case reports of occupational exposure" (Kulle 1987, p. 919) At the time the study was conducted, occupational exposure levels ranged from <0.1 to >5.0 ppm, and indoor residential exposure levels ranged from <0.1 to >4.0 ppm. Risks to subjects were minimized by selecting levels that did not exceed the then-existing Occupational Safety and Health Administration (OSHA) permissible exposure level of 3 ppm formaldehyde. Subjects' health was evaluated prior to the study, subjects with recent illnesses that could put them at higher risk of irritation and negative health effects were excluded, and only non-smokers were enrolled.

The methacholine challenge is used to evaluate airway reactivity, such as asthma. It can cause tightening of the airways, dizziness, and discomfort, none of which are lasting effects.

b. ***Benefits.*** There were no directs benefits to the subjects participating in the study. Establishing a dose-response relationship between formaldehyde exposure and health effects will benefit society. This information can be used to evaluate both occupational and residential levels of formaldehyde and to inform regulatory decision making.

c. ***Risk-Benefit Balance.*** The potential societal benefits of identifying doses of formaldehyde at which irritation can occur outweighs the risks associated with the study.

4. Independent Ethics Review. The research was approved by the University of Maryland's Human Volunteers Research Committee (Kulle 1993, p. 325). No information about the ethics review is available.

5. Informed Consent. All subjects provided informed consent (Kulle 1987, p. 919). The consent form used in the study is not available.

6. **Respect for Subjects.** Subjects received financial compensation for their participation in the study. Subjects' confidentiality was protected; their identities are not revealed in the 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 by a person with the intention to submit the results to EPA.

The study was likely conducted in 1985 or 1986, received for peer review on August 7, 1986, and submitted for publication on March 27, 1987. This study was funded under a contract from the United States Department of Energy (DOE) (Kulle 1987, p. 923). The DOE and its predecessor agencies required contractors to comply with the requirements of the rules developed by the Department of Health and Human Services (HHS). The U.S. Department of Health and Human Services (HHS) and the U.S. Food and Drug Administration (FDA) adopted updated regulations for the protection of human subjects in research and clinical investigations in 1981. These regulations covered informed consent of subjects and protections for the rights and welfare of human subjects involved in research subject to these agencies' jurisdictions. While the research submitted did not cite to these standards, it is reasonable to apply the ethical standards of the 1981 amendments to this study as many institutional review boards followed these standards regardless of the research being reviewed. The rule requires review of proposed research and establishes criteria for approval of such research: risks to subjects must be minimized and reasonable in relation to anticipated benefits (to subjects and/or to resulting knowledge), equitable subject selection, documented informed consent from participants, protection of subjects' privacy and confidential data, and additional safeguards to protect vulnerable subjects.

Other prevailing ethical standards in the 1980s include the 1975 Declaration of Helsinki, the Nuremberg Code (1947), and the Belmont Report (1979). The Declaration of Helsinki underwent a number of revisions through 2013. 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).

In addition, FIFRA §12(a)(2)(P) was also in place at the time the research was conducted and requires that human subjects of research with pesticides be "fully informed of the nature and purposes of the test and of any physical and mental health consequences which are reasonably foreseeable" from their participation and freely volunteer to participate.

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

This article was identified by the EPA for consideration. 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.
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> In addition, FIFRA §12(a)(2)(P) applies. This passage reads:

> In general, [i]t shall be unlawful for any person . . . to use any pesticide in tests on human beings unless such human beings (i) are fully informed of the nature and purposes of the test and of any physical and mental health consequences which are reasonably foreseeable therefrom, and (ii) freely volunteer to participate in the test.

EPA has submitted this study for review by the HSRB in conformance with 40 CFR §26.1604.

Compliance with Applicable Standards

There is no evidence that any of the subjects enrolled in this study were under 18 years old, or that any of the female subjects were pregnant or nursing. Therefore, EPA's reliance on the research is not prohibited by 40 CFR §26.1703.

All subjects provided informed consent to participate in the study. The protocol underwent independent ethics review and approval by the Human Volunteers Research Committee at the University of Maryland. The study was designed with a dose that should allow measurable results without causing adverse effects beyond irritation. 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).

No information about the research protocol, consent form, or independent ethics review is available. However, absence of information does not indicate ethical deficiencies. There is no clear and convincing evidence to suggest that subject selection was inequitable, that any party exerted undue influence around subjects' decision to participate, or that there was a lack of fully informed, fully voluntary consent. Based on my evaluation of the research articles, I conclude 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. Therefore, reliance on this study is not prohibited by 40 CFR §26.1704(b)(2).

Based on the available information, the research appears to satisfy the requirements of FIFRA §12(a)(2)(P). Subjects received information about the study and gave informed consent before participating.

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