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

OFFICE OF CHEMICAL SAFETY AND
POLLUTION PREVENTION

February 24, 2023

MEMORANDUM

SUBJECT: Ethics Review of Research Mueller et al. Article Involving Intentional of Human Subjects to Formaldehyde

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

TO: Anita Pease, Director
Antimicrobials Division
Office of Pesticide Programs

REF: 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

I have reviewed available information concerning the ethical conduct of the research described in "Exposure study to examine the chemosensory effects of formaldehyde on hyposensitive and hypersensitive males." 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 consult with the Human Studies Review Board (HSRB) prior to relying on research.

Summary Characteristics of the Research

This study was designed to expose subjects to formaldehyde on five consecutive days and to 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, and 0.7 ppm) in an exposure chamber (p. 109). Researchers assessed "objective parameters (conjunctival redness, eye-blinking frequency, tear film break-up time, nasal flow rates) and subjective symptoms" (p. 108). During the exposure period, subjects rode a stationary bike at 80 watts for 15 minutes at predefined times, including two of the exposure peak periods if applicable. About 1 hour before each exposure period and 1 hour after each exposure period, subjects underwent an examination that involved "measurement

of nasal flow rates and self-reported tear film break-up time (sBUT), detection of CO_2 sensitivity, … determination of conjunctival redness (photo documentation), eye-blinking frequency (video recording, and recording of subjective symptoms and complaints" (p. 109). Subject symptoms were collected using the Swedish Performance Evaluation System (SPES) questionnaire. The eye-blinking frequency measurement and SPES questionnaire were completed inside the test chamber during the last 15 minutes of exposure; the remainder were collected outside the test chamber (p. 109). Subjects also completed the Positive and Negative Affect Schedule (PANAS) before the exposure period (p. 110). Following the five consecutive days of testing, subjects followed up with the study team at 1-, 2- and 3-weeks post exposure completion.

In addition to formaldehyde, subjects were exposed to varying concentrations of carbon dioxide (CO_2), because "nasal sensitivity to CO_2 was used as a surrogate for individual chemosensory sensitivity" (p. 108). For this portion of the study, "a 2-s application of three defined CO_2 concentrations (40, 60 and 80 percent by volume of CO_2) [was made] to volunteers' nasal mucosa by means of a gas delivery device" (p. 108). The concentration order was randomized and each concentration was tested three times. Subjects had a 30 second break between exposure periods. Subjects used a visual analogue scale (VAS) to indicate their sense of pain/sensory irritation. The CO_2 sensitivity measurements were taken before and after each formaldehyde exposure session, as well as during the 3 follow up visits following the formaldehyde exposure testing. This information was used to classify subjects as hyposensitive or hypersensitive.

To obtain more information and to confirm that the study underwent an independent ethics review, I attempted to contact Dr. Mueller, Dr. Triebig, and Dr. Bruckner. The correspondence I sent and received is included as Attachment 1. Dr. Triebig was able to provide a copy of the ethics approval of the protocol but could not locate any other records or raw data associated with this study. Dr. Bruckner did not respond to my requests. Dr. Käfferlein of the Institute for Prevention and Occupational Medicine noted that the raw data files associated with the study were not held by their institute, and that it was unlikely that the raw data were available anywhere given the age of the studies. This study was submitted for publication in 2011, and Germany's law requires retention of study data for 10 years. The requests to and exchanges with the researchers is Attachment 1 to this memo.

1. Value of the Research to Society:

The study had two aims: "to evaluate irritant FA [formaldehyde] effects on male volunteers, which were defined as hypo- or hypersensitive against sensory irritation" and "to examine potential genotoxic effects on human nasal mucosa and peripheral blood cells" (p. 108). The focus was to evaluate the effects at concentrations relevant to the workplace (p. 107). To investigate the levels at which specific effects occur, this study included by objective measurements of irritation and subjective ratings of discomfort (p. 24). Data from this study can be used to inform decision-making about levels of exposure to formaldehyde that cause adverse irritation-related effects.

2. Subject Selection:

a. Demographics. Forty-one adult males participated in the study. Subjects were "aged 32 ± 9.9 years on average" (p. 108).

b. Inclusion/Exclusion Criteria. Subjects were eligible to participate if they were adult, non-smoking males. The article notes that the exclusion criteria were "(1) eye-blinking frequency >20/min, (2) allergy and/or skin diseases, (3) drug abuse or consumption of alcohol >50g/day, (4) exposure to FA at workplace or at home, (5) diseases of the respiratory tract, metabolism or heart and (6) inadequate visus without visual aids" (p. 108).

c. Recruitment. The article did not contain information about subject recruitment.

3. Risks and Benefits:

a. Risks. The article notes that "[g]aseous formaldehyde [FA] is irritating to the eyes and respiratory tract by chemosensory effects and leads to reflex responses such as lacrimation, rhinorrhea, coughing, vasodilation and changes in rate and depth of respiration" (p. 107). These effects are temporary and resolve after the exposure to formaldehyde stops. Risks to subjects were minimized by selecting levels in line with the then-existing occupational exposure levels and based on animal and human study data. Additionally, risks were minimized by enrolling only subjects were healthy and non-smokers. Subjects with illnesses that could put them at higher risk of irritation and negative health effects were excluded.

Subjects were also exposed to carbon dioxide. To minimize the concentration of carbon dioxide applied, "subjects were instructed in velopharyngeal closure to seal off their nasal cavity from the mouth cavity and throat" (p. 108).

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 sensory irritation can occur outweighs the risks associated with the study.

4. Independent Ethics Review. The research was approved by the Ethics Committee of the Medical Faculty of the University of Heidelberg (p. 108). The University of Heidelberg currently holds a federal-wide assurance (FWA 00005282). The statute of the ethics committee that is available to the public notes that members are independent in the performance of their duties.[1] Dr. Triebig provided a copy of the ethics committee's approval of the protocol for research in German (Attachment 2).

5. Informed Consent. All subjects provided written informed consent (p. 108). The consent form was not available for review and the process was not described in the article.

[1] Statute of the Ethics Committee of the Heidelberg Medical Faculty and the Ethics Committee of the Medical Faculty Mannheim. December 1, 2009. Translated using Google Translate.

6. **Respect for Subjects.** Participant confidentiality was maintained during the study and subjects' privacy was not compromised in the report.

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 initiated on or after to the effective date of the amended Rule for the Protection of Human Subjects.

The study report notes that the research was "performed according to the Declaration of Helsinki" (p. 108). Some of the key principles from the 1996 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. Steps should be taken to avoid situations where subjects feel pressure to provide consent for any reason.

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.
>
> 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.

This research was conducted with formaldehyde. However, there is no indication that the formaldehyde used was a pesticide product or that the research was undertaken related to formaldehyde's pesticidal uses. Therefore, the provisions of FIFRA §12(a)(2)(P) related to the use of pesticide in tests on human beings did not apply to the conduct of this research.

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

Compliance with Applicable Standards

All subjects in the study were males over 18 years old. No pregnant or nursing women were enrolled in the study. Therefore, EPA's reliance on the research is not prohibited by 40 CFR §26.1703.

The research was conducted at a university by qualified staff. The research had a clear purpose and the protocol was reviewed and approved by an independent ethics committee. The study was designed with a dose that should allow measurable results without causing adverse effects beyond irritation. The risks to subjects were identified and considered, minimized where possible, and reasonable relative to the expected benefits of the research. The confidentiality of subjects was maintained during the study and in the publication of the article. All subjects provided written informed consent to participate. Because the study was conducted in accordance with the Declaration of Helsinki, it is reasonable to assume that subjects were free to withdraw at any time without penalty. Further, because this research was conducted by the same working group as the research described in the Lang et al. 2008 study, it is reasonable to assume that the same standards for consent and monitoring subject safety described in that publication were followed in this study. Based on these findings, 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).

The protocol, consent form, and all but one of the documents and records of independent ethics review were not available to EPA. 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, 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).

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.

Attachments

Attachment 1 – Compilation of EPA requests for information on the study
Attachment 2 – Ethics Committee Approval from Dr. Treibig (German)

Attachment 1
Correspondence Requesting Information on the conduct of Mueller et al.

Correspondence with Dr.Treibig

From: Gerhard Prof. Dr. Triebig
To: Arling, Michelle
Subject: Re: US Environmental Protection Agency questions - formaldehyde research
Date: Monday, January 23, 2023 5:04:39 AM
Attachments: image001.png

Good Morning Michelle Arling,

a few days ago I`ve received the notice of the sponsor of our study ( Verband der Deutschen Holzwerkstoffindustrie) that the files were not found. I`m sorry to inform you about this and I`ve no further idea to get our data for you.

Many thanks for inviting me to attend the meeting , but I`m not further interested in formaldehyd.

Have a nice week and kind regards

Prof.Dr.G.Triebig

Am 17.01.2023 um 13:44 schrieb Arling, Michelle:

> Good morning Prof.Dr.G.Triebig,
>
> Thank you for looking for information about the study and providing this letter documenting that the ethical board approval of the study.
>
> I appreciate all of your assistance so far.
>
> We may be discussing these studies with our independent advisory committee in April. Would you like me to forward the details of the meeting (by Zoom/virtual) with you?
>
> Kind regards,
> Michelle
>
> Michelle Arling (she/her)
> Human Research Ethics Review Officer
> Office of Pesticide Programs (3106P)
> 1200 Pennsylvania Avenue NW MC 7501M
> Washington DC 20460
> 202-566-1260
> arling.michelle@epa.gov
>
> ---
>
> **From:** Gerhard Prof. Dr. Triebig <arbeitsmedizin@triebig.eu>
> **Sent:** Saturday, January 14, 2023 8:30 AM
> **To:** Arling, Michelle <Arling.Michelle@epa.gov>
> **Subject:** Re: US Environmental Protection Agency questions - formaldehyde research

Also Happy New Year to You.

There is little success: attached I`ll send the votum of the ethical board of the university.

The raw data of our studies are probabely stored at the university server and I`ve no chance o find them.

A copy of our second study however was given to the sponsor . The manager I`contacted will try to find the disk.

The problem is ,that the office moved some years ago and my former contact person has already retired from work.

I`ll inform you about the progress.

Best regards , Prof.Dr.G.Triebig

Am 09.01.2023 um 14:12 schrieb Arling, Michelle:

> Happy new year Dr. Triebig!
>
> I'm checking to see whether you've had any success contacting your colleagues about accessing files or data related to either of the studies I mentioned in my earlier email.
>
> Warm regards,
> Michelle
>
> Michelle Arling (she/her)
> Human Research Ethics Review Officer
> Office of Pesticide Programs (3106P)
> 1200 Pennsylvania Avenue NW MC 7501M
> Washington DC 20460
> 202-566-1260
> arling.michelle@epa.gov
>
> ---
>
> **From:** Gerhard Prof. Dr. Triebig <arbeitsmedizin@triebig.eu>
> **Sent:** Saturday, December 17, 2022 6:49 AM
> **To:** Arling, Michelle <Arling.Michelle@epa.gov>
> **Subject:** Re: US Environmental Protection Agency questions - formaldehyde research
>
> Dear Dr. Arling,
>
> thanks for your mail.

as you already know , I`m retired from university of Heidelberg since several years.

Answers to your questions : The studies were approved by the ethical comittee of this university.

I`ve only few documents , but not the raw data.

However I`ll contact my co-workers to get some more informations and answer you in january next year.

Best regards

Prof.Dr.G.Triebig

Am 16.12.2022 um 18:14 schrieb Arling, Michelle:

> Dear Dr. Triebig,
>
> I'm writing from the United States Environmental Protection Agency. My name is Michelle Arling and I work at the US Environmental Protection Agency as the Human Research Ethics Review Officer in the Office of Pesticide Programs. My colleagues and I are reviewing two publications that were conducted under your direction at the University of Heidelberg. The articles are:
>
> 1. *Formaldehyde and chemosensory irritation in humans: A controlled human exposure study* (Regulatory Toxicology and Pharmacology 50(2008) 23-36).
> 2. *Exposure study to examine chemosensory effects of formaldehyde on hyposensitive and hypersensitive males* (Int Arch Occup Environ Health (2013) 86:107–117)
>
> We're looking at the results of these publications in our assessment of the risks of formaldehyde as a pesticide as well as part of our assessment under the Toxic Substances Control Act. In addition, the EPA's regulation of human studies requires us to evaluate studies' scientific and ethical conduct before we can rely on them in risk assessments.

I have a few questions about the data presented in the articles, as well as about the ethical conduct of the studies. In addition, my colleagues and I are interested in obtaining the raw data and any records associated with consent and review by the ethics board from the study if possible. I was hoping that you or someone at your institute would have the raw data or files associated with the research. Are you the appropriate person to direct the EPA's questions to?

I've spoken with one of the primary investigators on the 2008 article, Dr. Isabelle Lang-Zwosta, who noted that she did not own the raw data and could not share it. She suggested that I reach out to your institution as well as the University of Heidelberg, where the research was conducted.

If you're not the appropriate contact for this request, could you please let me know if there's someone else I should reach out to?

Thank you in advance for any assistance you can provide.

Michelle Arling (she/her)
Human Research Ethics Review Officer
Office of Pesticide Programs (3106P)
1200 Pennsylvania Avenue NW MC 7501M
Washington DC 20460
202-566-1260
arling.michelle@epa.gov

From: Käfferlein Heiko Dr. <Heiko.Kaefferlein@dguv.de>
Sent: Friday, December 16, 2022 11:49 AM
To: Arling, Michelle <Arling.Michelle@epa.gov>
Subject: AW: US Environmental Protection Agency questions - formaldehyde research

Dear Dr. Arling,

thank you for your inquiry.

Actually, the two studies (I quickly checked them on Medline) were not carried out at our institute but at the Institute of Occupational Medicine at the University of Heidelberg. Nevertheless, I know the senior author of both studies, Dr. Gerhard Triebig, from my work as a DFG/MAK

member in Germany. He is retired since several years from the University of Heidelberg but still active as a consultant in occupational medicine. His most recent e-Mail address is/was arbeitsmedizin@triebig.eu.

Honestly, I have no idea whether he still has access to the (raw) files in Heidelberg. In addition, the Institute was closed (or assigned to a different institute/department) after his retirement. From a personal point of view, I doubt that the raw data is still available. Federal law prescribes raw data storage for a minimum of "only" 10 years in Germany. So, I don´t expect the raw data being available for the 2008 study. However, the second study from 2013 is "borderline" and the data must be stored "somewhere" at the University of Heidelberg. Otherwise, they are going to run into some issues

I suggest to contact Gerhard Triebig. He might be able to shed some light on the issue and may provide further details.

I hope this helps and I am truly sorry for not being able to provide more information.

With kind regards,
Heiko Käfferlein

Dr. rer. nat. Heiko Käfferlein
Head, Center of Toxicology
Phone: +49 30 13001-4401
Email: heiko.kaefferlein@dguv.de

Institute for Prevention and Occupational Medicine of the German Social Accident Insurance
Institute of the Ruhr University Bochum (IPA)
Deutsche Gesetzliche Unfallversicherung e.V. (DGUV)

Bürkle-de-la-Camp-Platz 1, 44789 Bochum, Germany | www.dguv.de/ipa
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Von: Arling, Michelle <Arling.Michelle@epa.gov>
Gesendet: Donnerstag, 15. Dezember 2022 21:38
An: heiko.kaefferlein@dguv.de
Betreff: US Environmental Protection Agency questions - formaldehyde research

Good afternoon Dr. Kaefferlein,

My name is Michelle Arling and I work at the US Environmental Protection Agency as the Human Research Ethics Review Officer in the Office of Pesticide Programs. My colleagues and I are reviewing two publications that I understand describe research that was funded by Germany's Institute for Occupational Medicine. The articles are:

1. *Formaldehyde and chemosensory irritation in humans: A controlled human exposure study* (Regulatory Toxicology and Pharmacology 50(2008) 23-36).
2. *Exposure study to examine chemosensory effects of formaldehyde on hyposensitive and hypersensitive males* (Int Arch Occup Environ Health (2013) 86:107–117)

We're looking at the results of these publications in our assessment of the risks of formaldehyde as a pesticide as well as part of our assessment under the Toxic Substances Control Act. In addition, the EPA's regulation of human studies requires us to evaluate studies' scientific and ethical conduct before we can rely on them in risk assessments.

I have a few questions about the data presented in the articles, as well as about the ethical conduct of the studies. In addition, my colleagues and I are interested in obtaining the raw data and any records associated with consent and review by the ethics board from the study if possible. Because the research was funded by your institute, I was hoping that you or someone at your institute would have the raw data or files associated with the research. Are you the appropriate person to direct our questions to?

I've spoken with one of the primary investigators, Dr. Isabelle Lang-Zwosta, who noted that she did not own the raw data and could not share it. She suggested that I reach out to your institution as well as the University of Heidelberg, where the research was conducted.

If you're not the appropriate contact for this request, could you please let me know if there's someone else I should reach out to?

Thanks in advance for any assistance you can provide.

Kind regards,

Michelle

Michelle Arling (she/her)
Human Research Ethics Review Officer
Office of Pesticide Programs (3106P)
1200 Pennsylvania Avenue NW MC 7501M
Washington DC 20460
202-566-1260
arling.michelle@epa.gov

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Prof. Dr. med. Dipl. Chem. Gerhard Triebig
Arzt für Arbeitsmedizin
Sozial- und Umweltmedizin
Betriebsarzt/Gutachter

Wolfstrasse 8
74915 Waibstadt-Daisbach
Tel.: 07261-2439
Fax.: 07261-9746530
E-Mail: arbeitsmedizin@triebig.eu

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Prof. Dr. med. Dipl. Chem. Gerhard Triebig
Arzt für Arbeitsmedizin
Sozial- und Umweltmedizin
Betriebsarzt/Gutachter

Wolfstrasse 8
74915 Waibstadt-Daisbach
Tel.: 07261-2439
Fax.: 07261-9746530
E-Mail: arbeitsmedizin@triebig.eu

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Prof. Dr. med. Dipl. Chem. Gerhard Triebig
Arzt für Arbeitsmedizin
Sozial- und Umweltmedizin
Betriebsarzt/Gutachter

Wolfstrasse 8
74915 Waibstadt-Daisbach
Tel.: 07261-2439
Fax.: 07261-9746530
E-Mail: arbeitsmedizin@triebig.eu

Email to Dr. Mueller

Arling, Michelle (she/her/hers)

From: Arling, Michelle
Sent: Monday, December 12, 2022 12:25 PM
To: joerg.mueller@gmx.de
Subject: US EPA Inquiry - 2013 Publication on Formaldehyde

Hello Mr. Mueller,

My name is Michelle Arling and I work at the US Environmental Protection Agency as the Human Research Ethics Review Officer in the Office of Pesticide Programs. Dr. Isabelle Lang-Zwosta shared your email address with me when we discussed her publication from 2008 involving similar work. My colleagues and I are reviewing a publication you authored, *Exposure study to examine chemosensory effects of formaldehyde on hyposensitive and hypersensitive males* (Int Arch Occup Environ Health (2013) 86:107–117). We're looking at the results of this publication in our assessment of the risks of formaldehyde as a pesticide as well as part of our assessment under the Toxic Substances Control Act. In addition, the EPA's regulation of human studies requires us to evaluate studies' scientific and ethical conduct before we can rely on them in risk assessments.

I have a few questions about the data presented in the article, as well as about the ethical conduct of the study. In addition, my colleagues and I are interested in obtaining the raw data from the study if possible. Are you the appropriate person to direct our questions to? If not, could you please put me into contact with one of the other authors: Gerhard Triebig or Thomas Bruckner? I've already reached out to Mr. Triebig as the corresponding author for the article, but have not received a response yet.

Thanks in advance for any assistance you can provide.

Kind regards,
Michelle

Michelle Arling (she/her)
Human Research Ethics Review Officer
Office of Pesticide Programs (3106P)
1200 Pennsylvania Avenue NW MC 7501M
Washington DC 20460
202-566-1260
arling.michelle@epa.gov

Correspondence regarding Dr. Bruckner

From: Arling, Michelle
To: Decker, Sebastian
Subject: RE: Contact information for Thomas Bruckner
Date: Tuesday, November 22, 2022 2:02:00 PM

Thank you very much for letting me know! Do you have any contact information (email address) for the Institute and Outpatient Clinic for Occupational and Social Medicine?

Warm regards,
Michelle

Michelle Arling (she/her)
Human Research Ethics Review Officer
Office of Pesticide Programs (3106P)
1200 Pennsylvania Avenue NW MC 7501M
Washington DC 20460
202-566-1260
arling.michelle@epa.gov

From: Decker, Sebastian <Sebastian.Decker@med.uni-heidelberg.de>
Sent: Tuesday, November 22, 2022 2:02 PM
To: Arling, Michelle <Arling.Michelle@epa.gov>
Subject: AW: Contact information for Thomas Bruckner

I am sorry for not having the possibility to help you. I don't know any of the colleagues you cited. My department has no cooperation with the Institute and Outpatient Clinic for Occupational and Social Medicine.

Kind regards

Sebastian Decker

Von: Arling, Michelle <Arling.Michelle@epa.gov>
Gesendet: Dienstag, 22. November 2022 19:36
An: Decker, Sebastian <Sebastian.Decker@med.uni-heidelberg.de>
Betreff: RE: Contact information for Thomas Bruckner

Thank you for letting me know about Thomas Bruckner's retirement. Both of the studies I am reviewing were conducted by Do you have contact info for any of the other authors who worked on the research I am reviewing? Both studies were conducted at the University of Heidelberg's Institute and Outpatient Clinic for Occupational and Social Medicine.

1. *Formaldehyde and chemosensory irritation in humans: A controlled human exposure study* (Regulatory Toxicology and Pharmacology 50(2008) 23-36).
2. *Exposure study to examine chemosensory effects of formaldehyde on hyposensitive and*

hypersensitive males (Int Arch Occup Environ Health (2013) 86:107–117)

The authors are:
Isabella Lang
Gerhard Triebig
Joerg Mueller

Michelle Arling (she/her)
Human Research Ethics Review Officer
Office of Pesticide Programs (3106P)
1200 Pennsylvania Avenue NW MC 7501M
Washington DC 20460
202-566-1260
arling.michelle@epa.gov

From: Decker, Sebastian <Sebastian.Decker@med.uni-heidelberg.de>
Sent: Tuesday, November 22, 2022 10:22 AM
To: Arling, Michelle <Arling.Michelle@epa.gov>
Subject: AW: Contact information for Thomas Bruckner

Hello Mrs. Arling,

I am very sorry. Thomas Bruckner was retired, so I don't have any contact data from him anymore.

Kind regards

Sebastian Decker

Von: Arling, Michelle <Arling.Michelle@epa.gov>
Gesendet: Dienstag, 22. November 2022 14:00
An: Decker, Sebastian <Sebastian.Decker@med.uni-heidelberg.de>
Betreff: Contact information for Thomas Bruckner

Hello Mr. Decker,

My name is Michelle Arling, and I work at the US Environmental Protection Agency in the Office of Pesticide Programs. My colleagues and I are reviewing some research involving formaldehyde conducted by Thomas Bruckner, and I have some questions I would like to ask him. I cannot find contact information for him online. Do you know whether he still has an active email address? If so, could you please put me in touch with him?

Thanks,
Michelle

Michelle Arling (she/her)
Human Research Ethics Review Officer
Office of Pesticide Programs (3106P)
1200 Pennsylvania Avenue NW MC 7501M
Washington DC 20460
202-566-1260
arling.michelle@epa.gov

Correspondence with Dr. Käfferlein

Arling, Michelle (she/her/hers)

From: Käfferlein Heiko Dr. <Heiko.Kaefferlein@dguv.de>
Sent: Friday, December 16, 2022 11:49 AM
To: Arling, Michelle
Subject: AW: US Environmental Protection Agency questions - formaldehyde research

Dear Dr. Arling,

thank you for your inquiry.

Actually, the two studies (I quickly checked them on Medline) were not carried out at our institute but at the Institute of Occupational Medicine at the University of Heidelberg. Nevertheless, I know the senior author of both studies, Dr. Gerhard Triebig, from my work as a DFG/MAK member in Germany. He is retired since several years from the University of Heidelberg but still active as a consultant in occupational medicine. His most recent e-Mail address is/was arbeitsmedizin@triebig.eu.

Honestly, I have no idea whether he still has access to the (raw) files in Heidelberg. In addition, the Institute was closed (or assigned to a different institute/department) after his retirement. From a personal point of view, I doubt that the raw data is still available. Federal law prescribes raw data storage for a minimum of "only" 10 years in Germany. So, I don´t expect the raw data being available for the 2008 study. However, the second study from 2013 is "borderline" and the data must be stored "somewhere" at the University of Heidelberg. Otherwise, they are going to run into some issues 😄

I suggest to contact Gerhard Triebig. He might be able to shed some light on the issue and may provide further details.

I hope this helps and I am truly sorry for not being able to provide more information.

With kind regards,
Heiko Käfferlein

Dr. rer. nat. Heiko Käfferlein
Head, Center of Toxicology

Phone: +49 30 13001-4401
Email: heiko.kaefferlein@dguv.de

Institute for Prevention and Occupational Medicine of the
German Social Accident Insurance
Institute of the Ruhr University Bochum (IPA)
Deutsche Gesetzliche Unfallversicherung e.V. (DGUV)

Bürkle-de-la-Camp-Platz 1, 44789 Bochum, Germany | www.dguv.de/ipa
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Von: Arling, Michelle <Arling.Michelle@epa.gov>
Gesendet: Donnerstag, 15. Dezember 2022 21:38
An: heiko.kaefferlein@dguv.de
Betreff: US Environmental Protection Agency questions - formaldehyde research

Good afternoon Dr. Kaefferlein,

My name is Michelle Arling and I work at the US Environmental Protection Agency as the Human Research Ethics Review Officer in the Office of Pesticide Programs. My colleagues and I are reviewing two publications that I understand describe research that was funded by Germany's Institute for Occupational Medicine. The articles are:

1. *Formaldehyde and chemosensory irritation in humans: A controlled human exposure study* (Regulatory Toxicology and Pharmacology 50(2008) 23-36).
2. *Exposure study to examine chemosensory effects of formaldehyde on hyposensitive and hypersensitive males* (Int Arch Occup Environ Health (2013) 86:107–117)

We're looking at the results of these publications in our assessment of the risks of formaldehyde as a pesticide as well as part of our assessment under the Toxic Substances Control Act. In addition, the EPA's regulation of human studies requires us to evaluate studies' scientific and ethical conduct before we can rely on them in risk assessments.

I have a few questions about the data presented in the articles, as well as about the ethical conduct of the studies. In addition, my colleagues and I are interested in obtaining the raw data and any records associated with consent and review by the ethics board from the study if possible. Because the research was funded by your institute, I was hoping that you or someone at your institute would have the raw data or files associated with the research. Are you the appropriate person to direct our questions to?

I've spoken with one of the primary investigators, Dr. Isabelle Lang-Zwosta, who noted that she did not own the raw data and could not share it. She suggested that I reach out to your institution as well as the University of Heidelberg, where the research was conducted.

If you're not the appropriate contact for this request, could you please let me know if there's someone else I should reach out to?

Thanks in advance for any assistance you can provide.

Kind regards,
Michelle

Michelle Arling (she/her)
Human Research Ethics Review Officer
Office of Pesticide Programs (3106P)
1200 Pennsylvania Avenue NW MC 7501M
Washington DC 20460
202-566-1260
arling.michelle@epa.gov

Attachment 2
Ethics Committee Approval from Dr. Treibig (German)

Medizinische Fakultät Heidelberg

Ethikkommission der Med. Fak. HD | Alte Glockengießerei 11/1 | D-69115 Heidelberg

Prof. Dr. med. Dipl.-Chem. G. Triebig
Institut und Poliklinik für Arbeits- und Sozialmedizin
Voßstr. 2
Gebäude 4040
69115 Heidelberg

11.05.2009
Str/wi

VOTUM
(Zustimmende Bewertung)

Unser Zeichen: S-054/2009 (Bitte stets angeben)

Titel: **Study of Chemosensory and Genotoxic Effects of Formaldehyde in normal and hypersensitive Volunteers**

Eingereichte Unterlagen:

Ersteinreichung:
Erstantragsformular, 18.02.2009
Zusammenfassung
Fax Versicherungsdienst Ecclesia
Probandeninformation (Vorauswahl)
Probandeninformation
Einverständniserklärung
Studienprotokoll
Bestätigung Aufwandserstattung
CD-ROM
Inhaltliche Nachreichung:
Schreiben vom 08.04.2009
Geänderte Probandeninformation
Geänderte Einverständniserklärung
CD-ROM

Sehr geehrter Professor Triebig,

mit den Änderungen bzw. Ergänzungen in den oben näher bezeichneten Dokumenten wurden die im Votum vom 17.03.2009 genannten Empfehlungen der Ethikkommission berücksichtigt. Damit liegt die **Zustimmung** der Kommission zu der o.g. Untersuchung vor.

Unabhängig vom Beratungsergebnis macht die Ethikkommission Sie darauf aufmerksam, dass die ethische und rechtliche Verantwortung für die Durchführung einer Studie beim Leiter der Studie und bei allen teilnehmenden Ärzten liegt.

Wir wünschen Ihnen bei der Durchführung des Projektes viel Erfolg.

Mit freundlichen Grüßen

Prof. Dr. med. Thomas Strowitzki
Vorsitzender der Ethikkommission

Ethikkommission
Medizinische Fakultät Heidelberg

Alte Glockengießerei 11/1
D-69115 Heidelberg
☎ +49 (0) 6221 / 33 8 22 0 (Empfang)
🖷 +49 (0) 6221 / 33 8 22 22
ethikkommission-k@med.uni-heidelberg.de
www.medizinische-fakultaet-hd.uni-heidelberg.de/ethikkommission

Vorsitz:
Prof. Dr. med. Thomas Strowitzki

Stellv. Vorsitz:
Prof. Dr. med. Johannes Schröder
Prof. Dr. med. Rainer Mattern

Geschäftsleitung:
Dr. med. Verena Pfeilschifter
☎ +49 (0) 6221 / 33 8 22 10
🖷 +49 (0) 6221 / 56 3 36 15
Verena.Pfeilschifter@med.uni-heidelberg.de

ANSPRECHPARTNER:

AMG-Studien federführend:
Anne-Katrin Schumacher,
Dipl.-Inform. med,
☎ +49 (0) 6221 / 33 8 22 13
🖷 +49 (0) 6221 / 33 8 22 22
Anne-K.Schumacher@med.uni-heidelberg.de

AMG-Studien beteiligt:
Stefanie Schneider, Dipl. Inf. (FH)
☎ +49 (0) 6221 / 33 8 22 14
🖷 +49 (0) 6221 / 33 8 22 22
Stefanie.Schneider2@med.uni-heidelberg.de

Sonstige und MPG-Studien:
Esther Wirth,
Betriebswirtin (WA), Dipl. Ing. (FH)
☎ +49 (0) 6221 / 33 8 22 11
🖷 +49 (0) 6221 / 33 8 22 22
Esther.Wirth@med.uni-heidelberg.de

Rechnungswesen:
Katharina Schäfer, Industriekauffrau
☎ +49 (0) 6221 / 33 8 22 12
🖷 +49 (0) 6221 / 33 8 22 22
Katharina.Schaefer@med.uni-heidelberg.de

Empfang:
Martina Jenner, DV-Kauffrau
☎ +49 (0) 6221 / 33 8 22 0
🖷 +49 (0) 6221 / 33 8 22 22
Martina.Jenner@med.uni-heidelberg.de

Qualitätsmanagement:
Dr. med. Verena Pfeilschifter
Qualitätsmanagerin (DGQ)
Anne-Katrin Schumacher
Assistenz

399893 QM

Bankverbindung:
Baden-Württembergische Bank Stuttgart
Konto-Nr.: 7421 500 429
BLZ: 600 501 01
SWIFT/BIC Code: SOLADEST
IBAN-Nr.: DE 64600501017421500429