



Formaldehyde Council

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EPA East – Room 6428 Attn: Section 8(e)
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington DC 20460-001

Contains No CBI

**Re: Formaldehyde (CASRN 50-00-0); Informal communication on
'Formaldehyde and chemosensory irritation in humans' study findings**

Dear Sir or Madam:

On behalf of its member companies, the Formaldehyde Council, Inc. (FCI) is submitting this letter to report on informal communications on October 3, 2006, concerning a study to be entitled 'Formaldehyde and chemosensory irritation in humans.' The study is being conducted at the Institute and Out-patient Clinic of Occupational and Social Medicine, University of Heidelberg, Germany. The study authors are Gerhard Triebig, M.D., S. Sc., Steffen Sandermann, M.D., Thomas Bruckner, M. Sc. and Isabelle Lang. The study protocol is attached.

This information is being supplied pursuant to current guidance issued by the Environmental Protection Agency (EPA) indicating EPA's interpretation of section 8(e) of the Toxic Substances Control Act (TSCA). Neither FCI nor any member company has made a determination as to whether a significant risk of injury to human health or the environment is actually presented by the findings. FCI believes that submission of this information is consistent with good product stewardship. FCI will provide the agency with the final report when it is obtained.

It appears that the study authors have tentatively concluded that there are no substance-related effects for reaction time, nasal resistance, nasal flow or bronchial obstruction for exposed subjects. There is slight objective eye irritation after 195 minutes of exposure at 0.5 parts per million coupled with peak exposure of 1 ppm. With regard to ocular irritation, the study authors are trying to distinguish between subjective and objective responses. Objective evidence of ocular irritation was observed only at the highest exposure level of 0.5 ppm coupled with 1 ppm peak exposure, which gave an indication of increased conjunctive redness and a significant increase in blinking frequencies, the most sensitive objective parameter.

If you have any questions regarding this submission, please do not hesitate to contact FCI.

Sincerely,

Betsy Natz



Enclosure



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Formaldehyde and chemosensory irritation in humans

Table of content

Chapter:	page
1. INTRODUCTION AND SCIENTIFIC FUNDAMENTALS	1
2. AIM OF THE STUDY	1
3. TESTING PROCESS	2
3.1. METHODS	3
3.2. EFFECTS	5
3.3. SIDE EFFECTS	6
4. STUDY DESIGN	6
5. PROCESS OF RANDOMISATION	6
6. INCLUSION CRITERIA	6
7. EXCLUSION CRITERIA	6
8. COURSE OF STUDY	6
9. CONCOMITANT THERAPY	7
10. LABRATORY SAFETY MEASURES	7
11. WITHDRAWAL CRITERIA	8
12. STATISTICS	8
13. QUALITY ASSURANCE	8
14. CHANGES OF THE PROTOCOL	9
15. ETHICAL AND LEGAL ASPECTS	9
15.1. ETHICAL ASPECTS	9
15.2. LEGAL ASPECTS	9
16. TIMELINE	9
17. LITERATURE	10
18. SIGNATURES	11

1. Introduction and scientific fundamentals

The proposed Occupational Exposure Limits (OELs) for formaldehyde (FA) vary considerably in various industrial countries. They range from lowest 0.3 (for instance Denmark) to 2.0 ppm (UK/HSE).

In Germany the MAK Commission has in 2000 recommended, to categorize FA as carcinogenic to humans. However the cancer risk was evaluated as follows: "No significant contribution to human cancer risk is expected provided the MAK value is observed ..." (DFG 2000/2004).

The MAK value, which is related to an eight hours exposure over 40 years of worklife, was set at 0.3 ppm with the peak category II (DFG 2004). This means, that the excursion factor is 2 (0.6 ppm) for four times of 15 minutes per working shift. The relevant effect for this OEL was irritation to the upper respiratory tract and the eyes.

The current OEL by law (Gefahrstoffverordnung) is set at 0.5 ppm.

Therefore it is of interest to identify those FA concentrations in the air which do not cause health effects in humans related to the most sensitive chemo-sensory effects. This is in accordance with the estimation of a NOEL (No Observed Effect Level) or LOEL (Lowest Observed Effect Level).

PAUSTENBACH and coworkers (1997) reviewed the older literature (published until 1995) on this topic. They concluded (1997) 1.0 ppm was determined to be an acceptable ceiling value (CV) for periods up to 15 min in duration and this is not expected to cause any eye irritation in at least 75 % of the workers. An OEL-CV of 1.0 ppm is the maximum concentration to which workers may be exposed. The authors acknowledged that the primary bases for their recommendations were the controlled human studies, since other data suffered from numerous possible confounding factors.

2. Aim of the study

The main objectives of the study are to examine possible health effects such as odor perception, irritations of mucous membranes of the eyes and upper respiratory tract as well as basic neuropsychologic functions during exposure to formaldehyde vapours in low concentrations. In this context the NOEL/LOEL has to be determined.

Additionally, the effects should be examined if and to which degree they will be modified by adaptation, habituation and personality factors.

Furthermore cytogenetic examinations, such as protein crosslinks and micronucleus, will be performed.

3. Testing process

The volunteers will be exposed in groups of 4 to 5 persons in a chamber (5 x 3 x 2.5 m) according to the following scheme (see page 7).

Temperature and humidity will be controlled and adjusted to normal conditions. Maximum air flow is 180 m³/h. Air exchange rate depends mainly on the possibility to reach constant formaldehyde levels.

FA vapours are generated by passing air through an oven in which paraformaldehyde is heated to about 75° C. The FA concentrations in the chamber will be measured in two ways.

First FA is monitored continuously with a commercial available voltametric sensor (Ansyco GmbH, Karlsruhe).

Second FA will be measured by collecting air samples and analyzing with the DNPH method according to DFG method. The detection limit is 15 µg/m³ (≈ 0.01 ppm).

Within a preliminary study formaldehyde will be determined to ascertain, that

- the background level in the chamber is near “zero” or below the detection limit of the method.
- stable FA concentrations in the chamber can be reached.
- an almost homogenous distribution is possible.

The exposures will be performed in random order and in a double blind fashion cross over design. This means, that FA-concentration will vary by chance and the volunteers and examiners do not know the FA-concentrations in the chamber. During the study it may be necessary, that one examiner has to control the exposures too.

To simulate the situation of real workplaces, the subjects will perform bicycle exercises (around 80 watts) for 15 minutes three times within 4 hours.

In order to differentiate between odor and sensory effect FA will be masked by addition of ethylacetate.

Ethylacetate (EA) has a pleasant odor with a threshold level of about 10 ppm. Irritations of mucous membranes are reported to occur at concentrations of 400 ppm and above.

Before starting the study, it was tested, that a EA concentration of 20 ppm will mask formaldehyde concentrations of 1.0 ppm sufficiently.

EA will be measured continuously by photoionisation analyses (Auer MSA, PPM, Berlin).

EA concentrations will be documented together with the analytical data.

3.1. Methods

The examinations will be performed before, during rest (if necessary) and at the end of daily exposure.

The following effects will be investigated:

Symptoms:

- I. Standardized Questionnaire of perception of odor and complaints of irritation and annoyance (German version of SPES Questionnaire (SEEBER et al. 2002)).

Sham-symptoms (heart palpitations, double vision) according to KULLE et al. (1987) will be included.

Eyes:

- II. Blinking frequency using video technique (as described by KLENØ and WOLKOFF (2004))
- III. Hyperemia by use of slit-lamp and photographic documentation

Nose:

- IV. Nasal flow rates by anterior rhinomanometry before and after daily exposure
- V. Nasal lavage with isotonic sodium chloride solution and measurement of various biomarkers such as interleukin IL 1, IL 6, tryptase, eosinophilic cationic protein (ECP) (HOFFMANN et al. 2004, KLIMEK et al. 2002, NORBÄCK und WIESLANDER 2002)

The analyses will be performed in cooperation with Prof. Dr. Klimek/Dr. Pfaar (Wiesbaden).

Lavage will be done several times:

- during pre-exposure examination
- on day 1 before exposure
- on day 10 after exposure
- week 1, 2 and 3 after exposure

- VI. Assessment of olfactory function using "Sniffin' Sticks" according to HUMMEL et al. 1997 and KOBAL et al. 1996 resp. This test will be performed on several time
- during pre-exposure examination
 - on day 1 before exposure
 - on day 10 after exposure
 - week 1, 2 and 3 after exposure

Mouth:

- VII. Smear of the mucosa of the mouth for cytogenetic testing. The cell material will be fixed according standard procedures and stored until analyses of crosslinks. This will be done in cooperation with Prof. Dr. Speit, Ulm. Smear test will be done several times
- during pre-exposure examination
 - day 1 before exposure
 - day 10 after exposure
 - week 1, 2, 3 after exposure

Airways/Lungs:

- VIII. Bodyplethysmography will be done to measure airways resistance and flow-volume-curve on day 1 before and on day 10 after exposure.
- IX. Exhaled breath condensate (EBC) will be sampled using a standardized method (Eco Screen, Jaeger-Toennies Co.).

- EBC will be done several times
- during pre-exposure examination
 - day 1 before exposure
 - day 10 after exposure
 - week 1, 2, 3 after exposure

The samples will be stored deep frozen (~ minus 70° C) until analyses, which will be done in the laboratory of Prof. Dr. Kraus, Aachen.

Selection of biomarkers will be done in cooperation with Prof. Dr. Kraus considering actual knowledge as published by ANTCZAK et al. 2002, GOLDONI et al. 2004 and MUTLU et al. 2001).

Neuropsychologic examination:

- X. Simple and choice reaction time as well as tapping will be tested with Wiener Testsystem on several times
 - during pre-exposure exam.
 - day 1 to 10 before and after exposure
 - week 1, 2, 3 after exposure
- XI. Intelligence level will be determined with a standardized procedure (MWT-B) (LEHRL 1989)
- XII. To control for personality factors, such as mood disposition, stress, annoyance, the PANAS will be applied to volunteers. PANAS is a Self-report stress scale (WATSON and PENNEBAKER 1989, KROHNE et al. 1996). According to our experiences around 50 % will show "positive" and 50 % "negative" mood disposition (HOFFMANN et al. 2004).

3.2. Effects

The MAK value, which is related to an eight hours exposure over 40 years of worklife, was set at 0.3 ppm with the peak category II (DFG 2004). This means, that the excursion factor is 2 (0.6 ppm) for four times of 15 minutes per working shift. The relevant effect for this OEL was irritation to the upper respiratory tract and the eyes.

The following dose-effect relationships are known:

0,1 – 0,3 ppm	odor perception
0,5 – 2,0 ppm	irritation of mucous membranes of the eyes and upper respiratory tract
2,0 – 5,0 ppm	no hints for obstructive airway diseases or sensitising

According to the actual scientific knowledge only odor perception and transient irritation of mucous membranes of the eyes and upper respiratory tract are expected in this study. These effects are reversible within minutes after exposure has stopped.

3.3. Side effects

Under this conditions no side effects are expected.

4. Study design

The exposures will be performed in a double blind fashion cross over design. This means, that FA-concentration will vary by chance and the volunteers and examiner do not know the FA-concentrations in the chamber.

5. Process of randomisation

not applicable

6. Inclusion criteria

The suggested number of volunteers is a result of considerations of the power of the study (see 12) and current experiences of our study group (HOFFMANN et al. 2004).

Selection criteria are:

- 20 healthy volunteers (10 men, 10 women)
- age range: 20 to 40 years
- non smokers

Ex-smokers, who have quit smoking at least 3 years ago, can also participate.

To objectify the smoking status, cotinine in urine will be analysed. A basic medical examination will provide, that the volunteers are in good health condition.

7. Exclusion criteria

Exclusion criteria are: severe allergy, manifest skin or airways disease, acute infection, current smokers, wear of contact lenses or spectacles, more than 50 grams alcohol per day, present use of psychopharmacologic medication, non-native German language.

8. Course of study

EXPOSURE SCHEME

I. Exposure without PEA

Day*	FA-concentration (ppm)	time (h)	activity
1	0	4	4 x 15 min.

2	0.15	4	4 x 15 min.
3	0.30	4	4 x 15 min.
4	0.30 plus 4 x peaks of 0.6 for about 15 minutes	4	4 x 15 min.
5	0.50	4	4 x 15 min.
6	0.50 plus 4 x peaks of 1.0 for about 15 minutes	4	4 x 15 min.

* random sequence

II. Exposure with PEA

Day*	FA-concentration (ppm)	time (h)	activity
7	0	4	4 x 15 min.
8	0.3	4	4 x 15 min.
9	0.5	4	4 x 15 min.
10	0.5 plus 4 x peaks of 1.0 for about 15 minutes	4	4 x 15 min.

* random sequence

Under this conditions the examination of 20 subjects will take around 15 weeks.

9. Concomitant therapy

In case of intercurrent disease the participant will be excluded from the study. Concomitant therapy is not possible.

10. Laboratory safety measures

not applicable

11. Withdrawal criteria

Individual:

Before the study begins participants will be informed that they can leave the chamber ahead of time under the following circumstances: unpleasant odor, dyspnea, severe hyperemia of mucous membranes, severe nasal flow, cough, expectoration, severe tear flow. Withdrawal from participation is also possible at any time without giving a reason.

Entire Study:

The study will be discontinued if severe irritation of mucous membranes or other adverse effects are observed.

12. Statistics

The power calculation is based on a power primer of the University of Münster, available in the internet (<http://medweb.uni-muenster.de/institute/imib/lehre/skripte/biomathe/bio/bio.html>). Following international standards the general assumptions are a power of 80% and an α of 0.05.

If differences in complaints between two exposure conditions are around one standard deviation, 10 participants are needed. If the differences will be only 0,5 standard deviation, 33 participants would be necessary.

Therefore 20 persons should be enough to detect medium effects. However this number would not be enough to detect small effects.

According to the results of a chamber study with ammonia exposure and similar design, the chemosensory effects were close to one standard deviation (HOFFMANN et al. 2004).

The statistical analysis will be performed with the SPSS computer program.

13. Quality assurance

Quality assurance will be carried out by an independent unit (Dr. Knoell Consult GmbH, Dr. S. Mueller). The quality assurance will comprise the following tasks:

- Approval that the study protocol meets quality assurance needs
- Onsite inspection (monitoring) at the beginning and during the course of the study
- quality check of data in the Microsoft Access Database.

14. Changes of the protocol

Changes of the protocol will be given as written amendments. They will come into force after approval by the principal investigator, study physician and the sponsor's representative. Protocol changes will be distributed to the principal investigator, study physician, OA monitor and sponsor's representative within a few days.

15. Ethical and legal aspects

15.1. Ethical aspects

The study will be conducted in accordance with the actual version of the declaration of Helsinki from 1996. The participation in the study is voluntary. Agreement to participate in the study can be withdrawn at any time without giving a reason and without any disadvantages to the medical support.

Before the study begins, participants will be informed about the nature of the study orally and in paper. Especially the advantages and the potential health risks within the study will be clarified. Agreement will be documented by signing the written informed consent.

In case of drop out the obtained data will be erased unless the participant agrees otherwise.

15.2. Legal aspects

The protocol was presented to the ethical commission of the Medical Faculty of the University of Heidelberg. The commission agreed on May, 10th, 2005, with the protocol and recommended minor modifications of the information sheet for the participants

The results of the study are handled absolutely confidential regarding legal requirements concerning confidential medical communication (Bundesdatenschutzgesetz).

Transmission of data to third party is not possible.

16. Timeline

The timeline is as follows:

- | | |
|--------------------------|--|
| - Sept. – Dec. 2005 | exposures/examinations |
| - Dec. 2005 | interim report |
| - Dec. 2005 – March 2006 | data entry into database/analysis/statistics |
| - April 2006 | first results |
| - July 2006 | draft final report |

17. Literature

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affectivity.
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18. Signatures

The study protocol has been reviewed and approved by

Date	Prof. Dr. G. Triebig (participal investigator)
Date	Dr. J. Geier (study physician)
Date	Dr. S.P. Mueller (QA monitor)
Date	Dr. A. Gamer (CEFIC sponsor representative)