Formaldehyde and chemosensory effects in hyper- and hyposensitive volunteers

G. Triebig, J. U. Mueller, T. Bruckner

Formaldehyde Science Conference
19-20 April 2012
Madrid, Spain
Objectives

to examine chemosensory effects of formaldehyde

- on hyper- and hyposensitive healthy, non smoking men
- symptoms and findings on eyes, nose and olfactory function
- exposed to concentrations typical for workplaces: up to 0.8 ppm
Subjects

- 41 men
- 32 +/- 10 years old
- students and unemployed persons
- exclusion criteria:
  - severe illness, insufficient German language skills, use of contact lens, exposure to formaldehyde

The Study was approved by the Ethics Committee of the Medical Faculty of the University of Heidelberg
Exposure

- Exposed on 5 consecutive days (Monday to Friday)
- 4 hours daily
- Five randomized formaldehyde concentrations / double-blinded
  - A: 0.0 ppm (control group)
  - B: 0.3 ppm with 0.6 ppm peak (4 x 15 min)
  - C: 0.4 ppm with 0.8 ppm peak (4 x 15 min)
  - D: 0.5 ppm
  - E: 0.7 ppm

Cumulative exposure: 8.3 ppm
Exposure chamber

- Total capacity about 30 m³ (Length: 4.3 m, Width: 2.9 m, Height: 2.4 m)
- Three ventilation fans were placed to generate homogenous concentrations
- To avoid a decrease of the formaldehyde concentration, the subjects had to cross a floodgate for entering the chamber.
exposure chamber

(Exposure chamber)

(Volunteers on cycle ergometer in exposure chamber)
Determination of Unspecific nasal Sensitivity (CO$_2$)

**CO$_2$-threshold measurement / Separation into „Sensitivity Groups“**

- CO$_2$ offers possibility to determine irritation of trigeminal nerve (=sensible nerve supply e.g. of the nose)
- CO$_2$-application at nasal mucosa evokes stinging, painful sensations (concentration- and sensitivity-dependent)
- provoked subjective pain intensities - marked on a VA-scale - were used for evaluation of “individual sum score”, mean value, median and quartiles.

- Separation on basis “of the individual sum score”
  - at median $\rightarrow$ 20 hyposensitive and 21 hypersensitive volunteers
  - at upper/lower quartile $\rightarrow$ 10 resp. 11 extremely hypo- /hypersensitive subjects

Example of the visual analogue scale (VAS) used for measurement of CO$_2$ threshold
Determination of Unspecific nasal Sensitivity (CO\textsubscript{2})

**CO\textsubscript{2}-threshold measurement / Separation into „Sensitivity Groups“**

- CO\textsubscript{2} offers possibility to determine irritation of trigeminal nerve (=sensible nerve supply e.g. of the nose)
- CO\textsubscript{2}-application at nasal mucosa evokes stinging, painful sensations (concentration- and sensitivity-dependent)
- provoked subjective pain intensities - marked on a VA-scale - were used for evaluation of “individual sum score”, mean value, median and quartiles.
- Separation on basis “of the individual sum score”
  - at median → 20 hyposensitive and 21 hypersensitive volunteers
  - at upper/lower quartile → 10 resp. 11 extremely hypo- /hypersensitive subjects

Example of the visual analogue scale (VAS) used for measurement of CO\textsubscript{2} threshold
Examinations:

- Subjective rating
  - Swedish Performance Evaluation System (SPES)
    - by Gamberale et al. 1989, German version by Seeber et al. 2002

- Photographs of the conjunctival redness
  - grading scale according to Cornea and Contact Lens Research Unit (CCLRU)

- Measurement of blinking frequency
  - new developed method by Ziegler et al. 2007

- Tear film break up time (stopwatch measurement)

- Olfactory function (n-butanol threshold, Sniffin-Sticks)

- Active anterior rhinomanometry
  - nasal flow and resistance

- PANAS (Positive and negative affectivity schedule)
1. Blurred Sight 0 1 2 3 4 5
2. Feeling of fainting or vertigo 0 1 2 3 4 5
3. Pain or pressure over the chest 0 1 2 3 4 5
4. Bad taste in the mouth 0 1 2 3 4 5
5. Sensation of bad air (quality) 0 1 2 3 4 5
6. Irritation of the throat 0 1 2 3 4 5
7. Headache 0 1 2 3 4 5
8. Coughing spells 0 1 2 3 4 5
9. Sensation of unpleasant taste 0 1 2 3 4 5
10. Nasty smell 0 1 2 3 4 5
11. Irritation of the skin 0 1 2 3 4 5
12. Dizziness 0 1 2 3 4 5
13. Shortness of breath 0 1 2 3 4 5
14. Nasty taste 0 1 2 3 4 5
15. Palpitations 0 1 2 3 4 5
16. Sensation of unpleasant smell 0 1 2 3 4 5
17. Nausea 0 1 2 3 4 5
18. Stink 0 1 2 3 4 5
19. Irritation of the nose 0 1 2 3 4 5
20. Itching nose 0 1 2 3 4 5
21. Dry nose 0 1 2 3 4 5
22. Running nose 0 1 2 3 4 5
23. Smarting nose 0 1 2 3 4 5
24. Diplocic images 0 1 2 3 4 5
25. Eyestrain 0 1 2 3 4 5
26. Itching eyes 0 1 2 3 4 5
27. Smarting eyes 0 1 2 3 4 5
28. Irritation of the eyes 0 1 2 3 4 5
29. Dry eyes 0 1 2 3 4 5
30. Watering eyes 0 1 2 3 4 5
31. Redness of the eyes 0 1 2 3 4 5

- 0 = not at all
- 1 = hardly at all
- 2 = somewhat
- 3 = rather much
- 4 = considerably
- 5 = very, very much
## SPES II

<table>
<thead>
<tr>
<th>Symptom group</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olfactory symptoms</td>
<td>Sensation of bad air (quality)</td>
</tr>
<tr>
<td></td>
<td>Nasty smell</td>
</tr>
<tr>
<td></td>
<td>Sensation of unpleasant smell</td>
</tr>
<tr>
<td></td>
<td>Stink</td>
</tr>
<tr>
<td>Nasal irritations</td>
<td>Irritation of the nose</td>
</tr>
<tr>
<td></td>
<td>Itching nose</td>
</tr>
<tr>
<td></td>
<td>Dry nose</td>
</tr>
<tr>
<td></td>
<td>Running nose</td>
</tr>
<tr>
<td></td>
<td>Smarting nose</td>
</tr>
<tr>
<td>Ocular irritations</td>
<td>Eyestrain</td>
</tr>
<tr>
<td></td>
<td>Itching eyes</td>
</tr>
<tr>
<td></td>
<td>Smarting eyes</td>
</tr>
<tr>
<td></td>
<td>Irritation of the eyes</td>
</tr>
<tr>
<td></td>
<td>Dry eyes</td>
</tr>
<tr>
<td></td>
<td>Watery eyes</td>
</tr>
<tr>
<td></td>
<td>Redness of the eyes</td>
</tr>
<tr>
<td>Shame symptoms</td>
<td>Palpitations</td>
</tr>
<tr>
<td></td>
<td>Diplocopic images</td>
</tr>
<tr>
<td>Symptom group</td>
<td>Symptoms</td>
</tr>
<tr>
<td>-------------------------</td>
<td>-----------------------------------------</td>
</tr>
<tr>
<td>Unspecific symptoms</td>
<td>Feeling of fainting or vertigo</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
</tr>
<tr>
<td>Not classified</td>
<td>Blurred sight</td>
</tr>
<tr>
<td></td>
<td>Irritation of the throat</td>
</tr>
<tr>
<td></td>
<td>Irritation of the skin</td>
</tr>
<tr>
<td>Taste symptoms</td>
<td>Bad taste in the mouth</td>
</tr>
<tr>
<td></td>
<td>Sensation of unpleasant taste</td>
</tr>
<tr>
<td></td>
<td>Nasty taste</td>
</tr>
<tr>
<td>Respiratory symptoms</td>
<td>Pain or pressure over the chest</td>
</tr>
<tr>
<td></td>
<td>Coughing spells</td>
</tr>
<tr>
<td></td>
<td>Shortness of breath</td>
</tr>
</tbody>
</table>
Examinations:

- Subjective rating
  → Swedish Performance Evaluation System (SPES)
    by Gamberale et al. 1989, German version by Seeber et al. 2002

- Photographs of the conjunctival redness
  → grading scale according to Cornea and Contact Lens Research Unit (CCLRU)

- Measurement of blinking frequency
  → new developed method by Ziegler et al. 2007

- Tear film break up time (stopwatch measurement)

- Olfactory function (n-butanol threshold, Sniffin-Sticks)

- Active anterior rhinomanometry
  → nasal flow and resistance

- PANAS (Positive and negative affectivity schedule)
Eye redness according to CCLRU

1 = very slight

2 = slight

3 = moderate

4 = severe
Examinations:

- Subjective rating
  → Swedish Performance Evaluation System (SPES)
    by Gamberale et al. 1989, German version by Seeber et al. 2002

- Photographs of the conjunctival redness
  → grading scale according to Cornea and Contact Lens Research Unit (CCLRU)

- Measurement of blinking frequency
  → new developed method by Ziegler et al. 2007

- Tear film break up time (stopwatch measurement)

- Olfactory function (n-butanol threshold, Sniffin-Sticks)

- Active anterior rhinomanometry
  → nasal flow and resistance

- PANAS (Positive and negative affectivity schedule)
examinations and volunteers

(Video recording of eye-blinking frequency)

(Test of olfactory function - „Sniffin Sticks“)
Examinations:

- Subjective rating
  - Swedish Performance Evaluation System (SPES)
    - by Gamberale et al. 1989, German version by Seeber et al. 2002

- Photographs of the conjunctival redness
  - grading scale according to Cornea and Contact Lens Research Unit (CCLRU)

- Measurement of blinking frequency
  - new developed method by Ziegler et al. 2007

- Tear film break up time (stopwatch measurement)

- Olfactory function (n-butanol threshold, Sniffin-Sticks)

- Active anterior rhinomanometry
  - nasal flow and resistance

- PANAS (Positive and negative affectivity schedule)
PANAS

<table>
<thead>
<tr>
<th>Positive affectivity</th>
<th>Negative affectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interested</td>
<td>Distressed</td>
</tr>
<tr>
<td>Excited</td>
<td>Upset</td>
</tr>
<tr>
<td>Strong</td>
<td>Guilty</td>
</tr>
<tr>
<td>Enthusiastic</td>
<td>Scared</td>
</tr>
<tr>
<td>Proud</td>
<td>Hostile</td>
</tr>
<tr>
<td>Alert</td>
<td>Irritable</td>
</tr>
<tr>
<td>Inspired</td>
<td>Ashamed</td>
</tr>
<tr>
<td>Determined</td>
<td>Nervous</td>
</tr>
<tr>
<td>Attentive</td>
<td>Jittery</td>
</tr>
<tr>
<td>Active</td>
<td>Afraid</td>
</tr>
</tbody>
</table>

Feelings and emotions were rated as follows: 1 = very slightly or not at all, 2 = a little, 3 = moderately, 4 = quite a bit, and 5 = extremely
Positive and Negative Affectivity Schedule (PANAS)

Statistical Evaluation of the PANAS

(= self description tool/questionnaire to characterise positive and negative personal patterns and traits of individuals)

- Participants offer a higher score for positive PANAS than for negative PANAS.

<table>
<thead>
<tr>
<th>Observations</th>
<th>PANAS</th>
<th>Mean ± SD</th>
<th>Median (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 41</td>
<td>positive affect (PA)</td>
<td>3.31 ± 0.60</td>
<td>3.50 (1.80 – 4.50)</td>
</tr>
<tr>
<td>n = 41</td>
<td>negative affect (NA)</td>
<td>1.46 ± 0.41</td>
<td>1.40 (1.00 – 2.90)</td>
</tr>
</tbody>
</table>

- PANAS parameters are comparable with published data in general population
- ´Negative affect´ (negative PANAS) was additionally used for statistical evaluation as covariate
- No relevant influences on subjective or objective findings could be detected
- Therefore the displayed results are based on the statistical calculation without considering ´negative affect´ as statistically covariate
Explanation of box whisker plots

- Maximum observation
- 75th percentile (upper quartile)
- Mean (specified with SYMBOL1 statement)
- Median
- 25th percentile (lower quartile)
- Minimum observation

Interquartile Range (IQR)
Results:

SPES sum score
Results:

Eye Irritation
Results:

Nasal Irritation
Results:

Olfactory Symptoms
# SPES II

<table>
<thead>
<tr>
<th>Symptom group</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Olfactory symptoms</strong></td>
<td>Sensation of bad air (quality)</td>
</tr>
<tr>
<td></td>
<td>Nasty smell</td>
</tr>
<tr>
<td></td>
<td>Sensation of unpleasant smell</td>
</tr>
<tr>
<td></td>
<td>Stink</td>
</tr>
<tr>
<td><strong>Nasal irritations</strong></td>
<td>Irritation of the nose</td>
</tr>
<tr>
<td></td>
<td>Itching nose</td>
</tr>
<tr>
<td></td>
<td>Dry nose</td>
</tr>
<tr>
<td></td>
<td>Running nose</td>
</tr>
<tr>
<td></td>
<td>Smarting nose</td>
</tr>
<tr>
<td><strong>Ocular irritations</strong></td>
<td>Eye strain</td>
</tr>
<tr>
<td></td>
<td>Itching eyes</td>
</tr>
<tr>
<td></td>
<td>Smarting eyes</td>
</tr>
<tr>
<td></td>
<td>Irritation of the eyes</td>
</tr>
<tr>
<td></td>
<td>Dry eyes</td>
</tr>
<tr>
<td></td>
<td>Watery eyes</td>
</tr>
<tr>
<td></td>
<td>Redness of the eyes</td>
</tr>
<tr>
<td><strong>Shame symptoms</strong></td>
<td>Palpitations</td>
</tr>
<tr>
<td></td>
<td>Diplopic images</td>
</tr>
</tbody>
</table>
Results:

Perception of Impure Air
Results:
Conjunctival Redness
Results:
Conjunctival Redness
Results:

Blinking Frequency
Results:
Tear film Break-Up Time
Results:
Nasal Flow
Results:

n-Butanol threshold
Results:

Sniffin‘ Sticks
Conclusions

- Formaldehyde concentrations of 0.7 ppm (constant) and 0.8 ppm (peak) are not associated with chemosensory effects on males hypo- and hypersensitive to CO2.

- Eye and olfactory symptoms occur at concentrations of 0.3 ppm (constant).

- Our results are in accordance with former review articles of Paustenbach et al. (1997) (1) and Arts et al. (2006) (2).

- Our results confirm the findings of Lang et al. (2008) (3), if the methodologic differences are considered.

References:
Differences to Lang et al. (2008)

- Varying FA concentrations: higher concentrations up to 1.0 ppm at peaks with Lang et al.
- Different examination times: SPES questionnaire (subjective symptoms) and eye blinking frequency performed - directly / with interval - after peak exposure or cycle ergometer unit.
- Statistically significant higher ´negative affectivity´ in the study of Lang et al. compared to present study.

- Different rating scales: visual analogue scale (VAS) vs. numerical rating scale (NRS)
  - Good correlation between the scales
  - VA scales are generally marked with lower values
Isabelle Lang, Thomas Bruckner, Gerhard Triebig: 
*Formaldehyde and chemosensory irritation in humans: A controlled human exposure study*, 

Joerg U. Mueller, Thomas Bruckner, Gerhard Triebig: 
*Exposure study to examine chemosensory effects of formaldehyde on hyposensitive and hypersensitive males*, 
Acknowledgement

We gratefully acknowledge the volunteers for their participation and the following colleagues for assistance and study advice: Lutz Buchholz, Heinz-Peter Gelbke, Joerg Haisser, Thomas Hummel, Michael Kentner, Christoph Klingmann, Jutta Martin, Benno Schuster, Guenter Speit, Rho Thiel, Andrea Vinzens.

The authors thank the FormaCare sector group of CEFIC, Brussels, the European Panel Federation, Brussels, and the Verband der Deutschen Holzwerkstoffindustrie e.V., Gießen, for their financial support of this study.
Thank you for your attention!