

**Institute and Outpatient Clinic for
Occupational and Social Medicine
University of Heidelberg**

**Formaldehyde and chemosensory
effects in normal, hyper- and
hyposensitive volunteers**

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Objectives

to examine chemosensory effects of formaldehyde

- on normal, hyper- and hyposensitive healthy, non smoking men and woman
- symptoms and findings on eyes, nose and olfactory function
- exposed to concentrations typical for workplaces: up to 1.0 ppm

Studies were approved by the Ethics Committee of the Medical Faculty of the University of Heidelberg

First study

Subjects

- 11 men and 11 woman
- 26 +/- 6 years old
- students, unemployed persons

Exposure

- Monday to Friday
- Two consecutive weeks (=10 days)
- Four hours daily
- Random order and double- blind fashion
- Masking with ethylacetat
- Examinations after 15 min, 120 min and 195 min of exposure

Exposure/ Concentrations

Scenario	Formaldehyde Continuous exposure (ppm)	Formaldehyde peaks (ppm)	EA (ppm)
1	0	-	-
2	0.15	-	-
3	0.3	-	-
4	0.3	4 x 0.6	-
5	0.5	-	-
6	0.5	4 x 1.0	-
7	0	-	12-16
8	0.3	-	12-16
9	0.5	-	12-16
10	0.5	4 x 1.0	12-16

Second Study

Subjects

- 41 men
- 32 +/- 10 years old
- unemployed persons

Exposure

- Exposed on 5 consecutive days (Monday – Friday), 4 hours daily
- 3 follow-up examinations at one-week-intervals
- five randomized formaldehyde concentrations:
 - concentration A: 0.0 ppm (control group)
 - concentration B: 0.3 ppm with 0.6 ppm peak (4 x 15 min)
 - concentration C: 0.4 ppm with 0.8 ppm peak (4 x 15 min)
 - concentration D: 0.5 ppm
 - concentration E: 0.7 ppm

Determination of Unspecific Sensitivity

CO2-threshold measurement / Separation into „Sensitivity Groups“

- CO2 offers possibility to determine irritation of trigeminal nerve (=sensible nerve supply e.g. of the nose)
- CO2-application at nasal mucosa evokes stinging, painful sensations (concentration- and sensitivity-dependent)
- provoked subjective pain intensities - marked on a VA-scale (by participant) - were used for mathematical calculation of "individual sum score" ("individual sensitivity score"), and for evaluation of mean value, median and quartiles.
- on basis of these "individual sum scores" of our volunteers

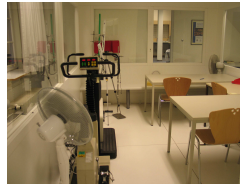
Separation into two subgroups

1. at median → 20 hyposensitive and 21 hypersensitive participants
2. at upper/ lower quartile → 10 resp. 11 extremely hypo- / hypersensitive subjects

Examinations:

- Subjective rating
 - Swedish Performance Evaluation System (SPES) by Gamberale et al. 1989, German version by Seeber et al. 2002
- Digital slit lamp photography: conjunctival redness
 - grading scale of the 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

examinations and volunteers



(Exposure chamber)



(Volunteers on cycle ergometer in exposure chamber)

examinations and volunteers



(Video recording of eye-blinking frequency)



(Test of olfactory function - „Sniffin Sticks“)

SPES I

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. Slink	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. Diplopic 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. Watery 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

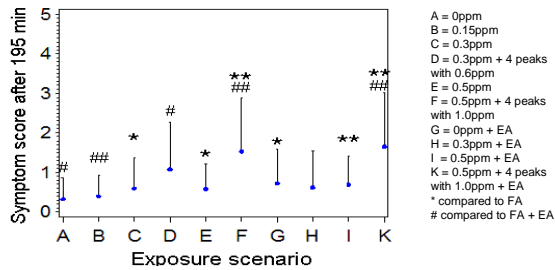
SPES II

Symptom group	Symptoms
Olfactory symptoms	Sensation of bad air (quality) Nasty smell Sensation of unpleasant smell Stink
Nasal irritations	Irritation of the nose Itching nose Dry nose Running nose Smarting nose
Ocular irritations	Eyestrain Itching eyes Smarting eyes Irritation of the eyes Dry eyes Watery eyes Redness of the eyes
Shame symptoms	Palpitations Diplopic images

SPES III

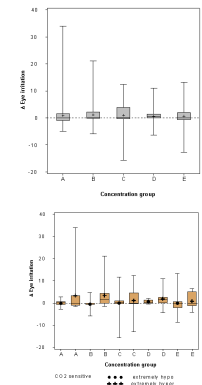
Symptom group	Symptoms
Unspecific symptoms	Feeling of fainting or vertigo Dizziness Nausea
Not classified	Blurred sight Irritation of the throat Irritation of the skin
Taste symptoms	Bad taste in the mouth Sensation of unpleasant taste Nasty taste
Respiratory symptoms	Pain or pressure over the chest Coughing spells Shortness of breath

Results Study I: Eye Irritation



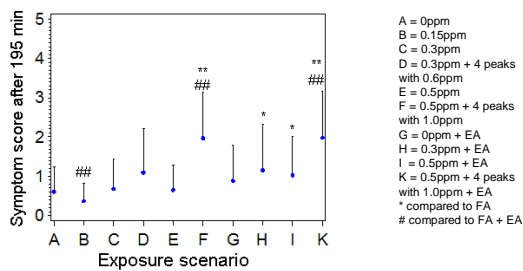
Results Study II: Eye Irritation

- Post-exposure 'Eye Irritation scores' are predominantly increased compared to values before exposure, *however*, without statistical significance and without a concentration-response-relationship.
- Comparison to the zero concentration and comparison between the sensitivity groups also revealed no statistical significant difference.



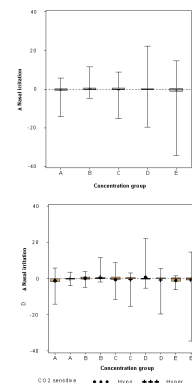
Results Study I: Nasal Irritation

(= combined organ related items/symptoms; e.g. burning-, running- or dry nose)



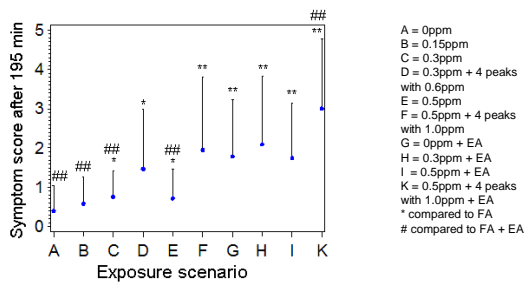
Results Study II: Nasal Irritation

- We found no uniform trend and no significant changes in post-exposure values. No concentration-response relationship could be detected.
- Comparison to the zero concentration and comparison between the sensitivity groups also revealed no consistent tendency.



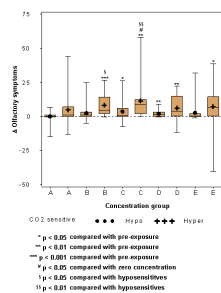
Results Study I: Olfactory Symptoms

(= combined organ related items/symptoms; e.g. stench, unpleasant smell or perception of impure air)
 "Olfactory Symptoms" is the very SPES-Subgroup with strongest increase of symptom-scores after exposure



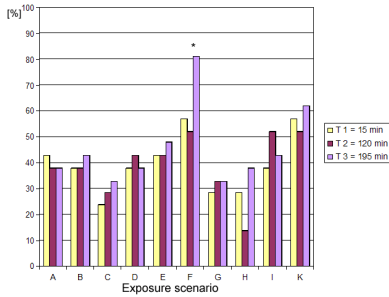
Results Study II: Olfactory Symptoms

- Generally, all volunteers indicate an increase of 'olfactory symptoms' after exposure (including control-group)
 - Higher increases were found in hypersensitive and extremely hypersensitive volunteers compared to hypo- / extremely hyposensitive counterparts.
- However*
- Comparison with zero-concentration reveals only few statistically significant differences and no consistent concentration-response relationship.
 - rather a 'situational effect' than attributable to formaldehyde effects → see following page



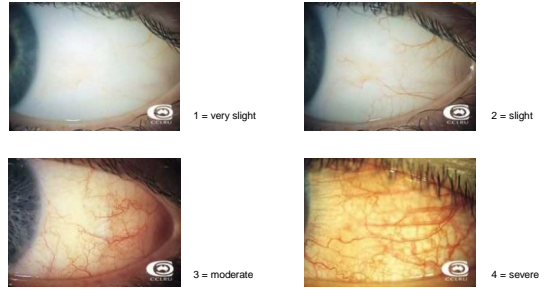
Results Study I: Conjunctival Redness

Eye redness grade 3



A = 0ppm
 B = 0.15ppm
 C = 0.3ppm
 D = 0.3ppm + 4 peaks with 0.6ppm
 E = 0.5ppm
 F = 0.5ppm + 4 peaks with 1.0ppm
 G = 0.6ppm + EA
 H = 0.3ppm + EA
 I = 0.5ppm + EA
 K = 0.5ppm + 4 peaks with 1.0ppm + EA
 * p < 0.05

Eye redness according to CCLRU

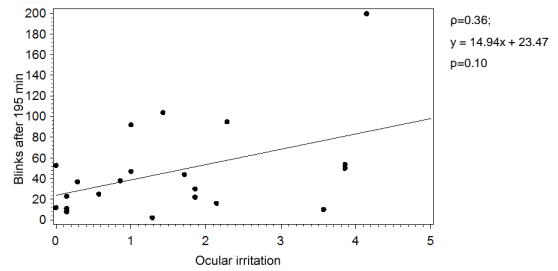


Results Study I: Blinking Frequency

Blinking frequency per 90 sec

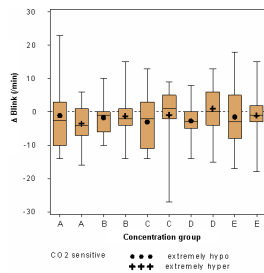
Formaldehyde concentration (ppm)	Mean blinking frequency \pm SD	Median	Range
0	28.2 \pm 30.2	20	3 – 120
0.15	31.2 \pm 31.4	21	3 – 145
0.3	27.8 \pm 24.7	21	4 – 118
0.3 + 4 peaks at 0.6	34.4 \pm 23.6	27	2 – 92
0.5	29.2 \pm 29.7	18	2 – 128
0.5 + 4 peaks at 1.0	46.3 \pm 45.6 *#	37	2 – 200
0 + EA	28.6 \pm 30.9	20	2 – 114
0.3 + EA	29.6 \pm 24.0	24	3 – 95
0.5 + EA	34.5 \pm 35.1	26	4 – 157
0.5 + 4 peaks at 1.0 + EA	45.2 \pm 45.0 *#	30	5 – 166

Results Study I: Correlation between blinking frequency and eye irritations



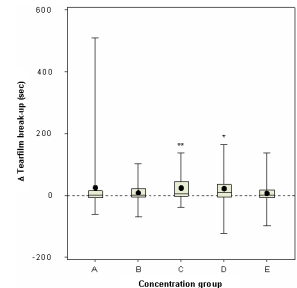
Results Study II: Blinking Frequency

- No concentration-dependent increase of eye blinking frequency after FA exposure
- No statistically significant differences
 - between pre- and post-exposure values
 - in comparison with zero concentration
 - between different sensitivity groups



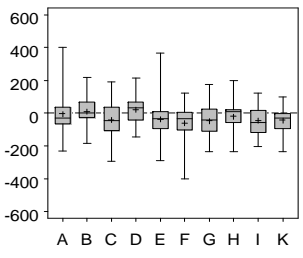
Results Study II: Tearfilm Break-Up Time

- We found an increase rather than a decrease of tear film break-up time after exposure.
- Comparison with control group and comparison between the sensitivity groups revealed no consistent tendency and no concentration-effect relationship



* p < 0.05 compared with pre-exposure
 ** p < 0.01 compared with pre-exposure

Results Study I: Nasal Flow



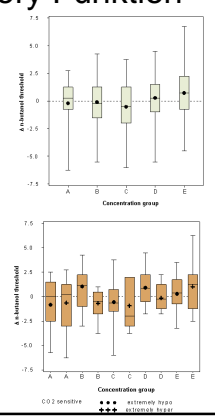
- A = 0ppm
- B = 0.15ppm
- C = 0.3ppm
- D = 0.3ppm + 4 peaks with 0.6ppm
- E = 0.5ppm
- F = 0.5ppm + 4 peaks with 1.0ppm
- G = 0ppm + EA
- H = 0.3ppm + EA
- I = 0.5ppm + EA
- K = 0.5ppm + 4 peaks with 1.0ppm + EA

Results Study II: Olfactory Funktion

n-Butanol threshold

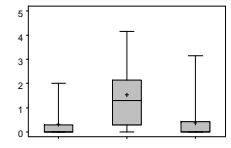
(performed daily before/after exposure and during the follow-up examinations)

- No consistent, concentration-dependent pre-/post-exposure change of n-butanol thresholds
- No significant differences compared to control group and no concentration-effect relationship detectable.
- No significant variation of n-butanol thresholds between different sensitivity groups
- Conclusion:
- no specific FA-effect detectable !



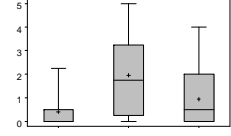
Results Study I: Time course

A) Ocular irritation



- A = No exposure
 - B = 0.5 ppm plus 4 peaks of 1.0 ppm
 - C = Next morning (about 16hrs after exposure)
- * p<0.05

B) Olfactory irritation



- A = No exposure
 - B = 0.5 ppm plus 4 peaks of 1.0 ppm
 - C = Next morning (about 16hrs after exposure)
- * p<0.05

Conclusions (1)

- Eye irritations are the most critical effects induced by formaldehyde vapors
- Blink frequency and redness of the eyes increased significantly at a concentration of 0.5 ppm with peaks of 1.0 ppm
- Peak exposure is more relevant to induce conjunctival effects
- Eye and olfactory symptoms started at concentrations of 0.3 ppm without peaks

Conclusions (2)

- No influence of gender on results
- No significant differences of specific effect parameters between hypo- and hyper-sensitive persons
- NOAELs of 0.5 ppm (constant exposure) and 0.8 ppm (shortterm peaks) are recommended
- Our results are in accordance with former review articles of Paustenbach et al. (1997) (1) and Arts et al. (2006) (2)

• 1 J. Toxicol. Environ. Health 50 (1997) 217-263
• 2 Regul. Toxicol. Pharmacol. 44 (2006) 144-160

Acknowledgement

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Publications

- Isabelle Lang, Thomas Bruckner, Gerhard Triebig:
Formaldehyde and chemosensory irritation in humans: A controlled human exposure study,
Regulatory Toxicology and Pharmacology 50 (2008) 23- 36.
- Joerg U. Mueller, Thomas Bruckner, Gerhard Triebig:
Exposure study to examine chemosensory effects of formaldehyde on hyposensitive and hypersensitive males,
International Archives of Occupational and Environmental Health, DOI 10.1007/s00420-012-0745-9.

