

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

**Styrene and Ototoxicity
Exposure Study in Volunteers**

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Objectives

to examine ototoxic effects in healthy volunteers

- after acute / subacute exposures
- to concentrations typical for workplaces in Germany
- to achieve a „No observed adverse effect level“

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

Subjects

- 11 healthy men
- 20 to 40 years old
- students, unemployed persons

- exclusion criteria: diseases of nose, ear, CNS, acute illness, medication, drugs, alcohol abuse, hearing loss in audiometry (>40 dB sum)

Exposures

- chamber (30 m³) with ventilation system
- 4 persons per session
- daily exposure for 6 hours
- styrene in air: 0, 20, 50 ppm
- additional exposure to industrial noise up to 85 dezibel via earphones

Examinations

before and after daily exposure

- inspection of ears, nose, throat
- pure tone audiometry: 0.125 to 16 kHz
- transitory evoked otoacoustic emissions (TEOAE)

- biomonitoring
 - blood: styrene
 - urine: mandelic acid, phenylglyoxylic acid, creatinine

**Exposure pattern and styrene in blood in
mg/L (mean ± SD)**

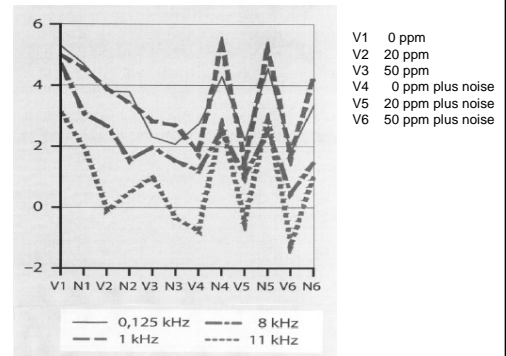
Day	Styrene in air [ppm]	Exposure to noise dB(A) 3 h	Styrene concentration in blood [µg/l]	
			Before	After
1	0	0	n.d.	n.d.
2	20	0	n.d.	327 ± 83
3	50	0	9 ± 3	815 ± 197
4	0	85	5 ± 3	5 ± 3
5	20	85	2 ± 2	352 ± 95
6	50	85	11 ± 4	850 ± 210

n.d. = not detectable

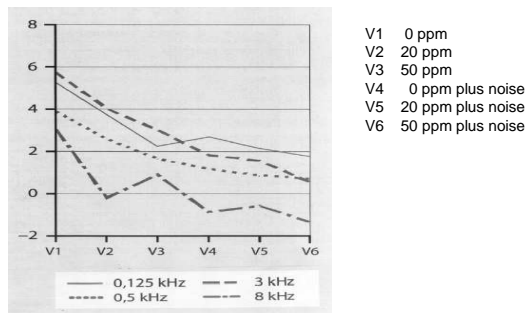
Exposure pattern and sum of MA and PGA in urine in mg/gram creatinine (mean and SD)

Exposure	before	after
0 ppm	8 ± 5	6 ± 3
20 ppm	9 ± 11	265 ± 78
50 ppm	45 ± 15	751 ± 206
0 ppm + 85 dB (A)	15 ± 13	12 ± 6
20 ppm + 85 dB (A)	13 ± 11	276 ± 119
50 ppm + 85 dB (A)	69 ± 48	693 ± 201

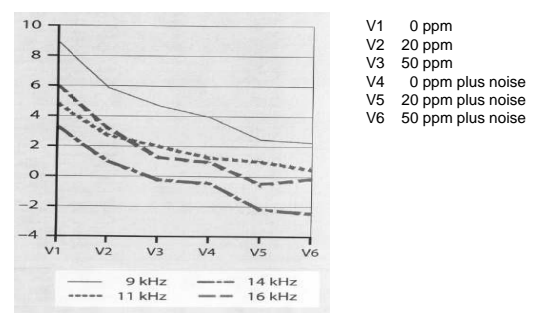
Results: Mean hearing thresholds before and after daily exposure



Results: Mean hearing thresholds before daily exposure



Results: Mean hearing thresholds before daily exposure



Results:

Differences of hearing thresholds before and after daily exposure in relation to intensity of exposure without (marked in black) and with (marked in red) noise exposure.

Frequency [kHz]	0 ppm + 85 dB (A)	20 ppm + 85 dB (A)	50 ppm + 85 dB (A)	ANOVA (p)
4,0	-1,6 ± 3,2*	-1,0 ± 3,1	-0,9 ± 2,4	0,43
4,0	3,1 ± 3,6 *	4,1 ± 3,2 *	2,8 ± 2,5 *	0,11
6,0	-1,1 ± 2,8	-0,5 ± 3,8	-0,2 ± 3,5	0,41
6,0	2,9 ± 3,4 *	2,2 ± 3,4 *	1,7 ± 2,7 *	0,32
8,0	-1,2 ± 2,8	0,6 ± 3,5	-1,3 ± 3,9	0,03
8,0	3,5 ± 4,1 *	3,3 ± 3,2 *	2,3 ± 4,2 *	0,22
10,0	-2,2 ± 4,0 *	-1,2 ± 2,4	-0,4 ± 2,3	0,02
10,0	1,1 ± 2,4 *	2,2 ± 2,5	1,1 ± 2,6	0,07
12,5	-1,6 ± 3,5	-1,3 ± 2,8	-0,1 ± 3,0	0,07
12,5	1,3 ± 2,5 *	2,1 ± 3,7 *	1,1 ± 2,3 *	0,18
16,0	-2,0 ± 3,7 *	-0,9 ± 3,3	0,1 ± 2,6	0,01 *
16,0	2,3 ± 3,8 *	2,3 ± 4,6	1,1 ± 3,0	0,23

Results: Number of detectable otoacoustic emissions

Exposure	before		after		p
	detectable	not detectable	detectable	not detectable	
0 ppm	35	1	35	1	1
20 ppm	35	1	36	0	0,31
50 ppm	36	0	34	2	0,15
0 ppm + 85 dB(A)	34	2	34	2	1
20 ppm + 85 dB(A)	36	0	35	1	0,31
50 ppm + 85 dB(A)	35	1	34	2	0,56

Results: Differences of amplitudes of TEOAE in relation to exposure

Exposure	0 ppm	20 ppm	50 ppm	ANOVA (p)
Styrene	-0,2 ± 1,1	-0,2 ± 1,0	-0,2 ± 1,2	0,98
Styrene ± 85 dB(A)	-0,5 ± 1,3	0,0 ± 1,2	0,0 ± 1,2	0,16

Results:

Correlation analyses of biomonitoring parameters (Styrene, MA, PGA) and effect parameters (differences of hearing thresholds / TEOAE):

There were no statistical significant correlations to indicate exposure-effect-relationships.

Conclusions

- Exposures to maximum styrene concentrations of 50 ppm over 6 hours for 5 consecutive days are not associated with ototoxic effects measurable with pure tone audiometry (high frequency) and otoacoustic emissions.
- Effect parameters were sensitive to detect noise induced reversible temporary threshold shift with a maximum of 4.5 dezibel at 3.0 kHz
- Combined styrene and noise exposure did not cause an additional effect exceeding threshold shift after noise alone.
- The study cannot exclude ototoxic effects of styrene, alone or in combination with noise, after chronic exposures.

Acknowledgement

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Publications of our working group

B.W. Lawton, J. Hoffmann, G. Triebig:
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