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Exposure to xylene and ethylbenzene

III. Effects on central nervous functions

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GAMBERALE, F., ANNWALL, G. and HULTENGREN, M. Exposure to xylene and ethylbenzene: III. Effects on central nervous functions. *Scand. j. work environ. & health* 4 (1978) 204—211. The effect of exposure to the solvent xylene on performance of tests of numerical ability, reaction time (simple and choice), short-term memory, and critical flicker fusion was studied in two separate laboratory series. In the first series fifteen healthy male subjects were studied individually on three separate occasions with exposure to 435 and 1,300 mg/m^3 xylene in inspired air and under control conditions. In a second series eight of the subjects were exposed to 1,300 mg/m^3 xylene in inspired air. This exposure period began with 30 min of work on a bicycle ergometer (100 W) and continued during the behavioral tests. The procedure was the same under control conditions. Each exposure period lasted 70 min. At certain times during exposure, samples of the subjects alveolar air were collected. Exposure to xylene did not cause any noticeable change in performance during the first laboratory series, when the subjects' total uptake of xylene was estimated to be on an average 180 and 540 mg, respectively. In the second series the physical work induced an increase in the total uptake up to an average of 1,200 mg. In this series clear evidence of performance decrement was observed in three of the performance tests.

Key words: behavioral effects, central nervous system, human exposure, industrial solvents, psychological functions, xylene.

The threshold limit value (TLV) for xylene is based on the irritating effect of the substance on the eyes and the mucous membrane of the nose and oral cavity (3, 13, 14). The TLV, which is set at 435 mg/m^3, is also considered to be below the concentrations presumed to cause acute effects on the central nervous system. We have, however, found no mention in the literature of any laboratory study where the effects of xylene on human central nervous functions have been studied.

In our previous studies of solvents (7, 8, 9, 10, 11, 12), acute effects on central nervous functions were observed even at relatively low concentrations. These concentrations were in some cases considerably lower than those generally thought to cause an acute effect. The aim of the present study was to examine the extent to which man's psychomotor and cognitive functions are affected by acute exposure to xylene.

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Table 1. Experimental design in series 1. The lowest and highest concentrations of xylene in inspiratory air during the trials are given.

Measurement occasion (d)	Exposure (mg/m³)		
	Group 1	Group 2	Group 3
1	air	1,267/1,333	423/443
2	423/443	air	1,267/1,333
3	1,267/1,333	423/443	air

METHODS

Subjects

Fifteen healthy males from 21 to 33 years of age participated as subjects. They were all either students or employees at the Department of Occupational Health.

Experimental design

Two series of experiments were conducted. In the first series, the 15 subjects were divided at random into three equally large groups. The subjects were studied individually under experimental conditions with exposure to two different concentrations of xylene [2] and under control conditions with exposure to ordinary atmospheric air. The three different trials for each subject were conducted at the same time of day on three different occasions every other day. The experimental sequence was balanced between the three groups, days and exposure levels according to table 1.

In the two experimental conditions the subjects were exposed for 70 min to xylene concentrations of 435 and 1,300 mg/m³ in inspiratory air. The gas mixture was supplied via a breathing valve with a very low resistance. The taste and smell of the gas was disguised by the introduction of a cannister containing menthol crystals into the tube to the mouthpiece. The concentration of xylene in inspiratory air was monitored continuously with the aid of a total hydrocarbon analyzer. The concentration of xylene in alveolar air was measured approximately every third minute during the first 35 min with a gas chromatographic technique. During the following 35 min, when five different performance tests were carried out, measurements were made after each test.

Under control conditions the air did not contain any xylene, but was disguised with menthol in the same manner. All other operations and measurements were carried out with the same apparatus, in the same manner, and in the same chronological order as under experimental conditions. Thus samples of alveolar air were also taken in the same manner.

Throughout series 1 the subjects were seated in a comfortable chair at a desk. On the first day the trial was preceded by instructions and practice on all tests. At the beginning of the exposure period the subject carried out a brief performance test, after which he spent approximately 30 min reading a newspaper. During the last 35 min of exposure five different performance tests were carried out, always in the same order. The subject's heart rate was checked regularly under all conditions with the aid of telemetric equipment (Medenik, Honeywell).

Eight of the subjects from the first experimental series also participated in the second series. The subjects were studied individually and were exposed to a xylene concentration of 1,300 mg/m³ during a 70-min period. Immediately prior to exposure the subject was given a brief performance test. During the first 30 min of the exposure period the subjects carried out moderately heavy physical work (bicycle ergometer 100 W). During these 30 min the volume of expiratory air was measured continuously with the Douglas

[2] The xylene used in both series had the following relative weight composition: p-xylene 12.8 %, o-xylene 12.1 %, m-xylene 54.4 %, and ethylbenzene 20.7 %.

bag technique. The xylene content was analyzed with a gas chromatographic technique. As in the first experimental series, samples of alveolar air were taken at certain times during the entire trial period. During the last 40 min of the exposure period the subject sat in a comfortable chair as in series 1. During the last 35 min of the exposure period the same performance tests were carried out as in the first experimental series. As previously, the subjects were also studied under control conditions without exposure to xylene. For half of the subjects this occurred two days before and for the other half two days after the exposure trial. Each subject's heart rate was monitored regularly during both trials with the aid of complete electrocardiography. Apart from the differences already mentioned, both experimental series were conducted with the same apparatus and techniques.

In both experimental series information was collected concerning the subjects' perception of the conditions. The subjects filled out a questionnaire after each trial, irrespective of whether exposure had taken place or not. They indicated their degree of sickness, headache, and intoxication with the aid of four fixed response alternatives. The subjects were also asked to assess their own condition as regards the following nine variables: calm—hurried, concentrated—distracted, active—passive, spry—tired, relaxed—tense, enterprising—unenterprising, collected—divided, alert—drowsy, energetic—lazy. The assessments were given with the aid of 7-point evaluation scales, where the extreme values constituted opposites. After the questionnaire had been completed, the subjects were asked to describe any further symptoms in their own words. Finally, after the last trial in each series, the subjects were asked whether they had noticed any difference between the various trial conditions. The purpose of this question was to ascertain the extent to which the menthol "camouflage" had been effective.

Performance tests

Critical Flicker Fusion. The test of critical flicker fusion (CFF) was conducted with a flicker-fusion apparatus from Lafayette Instrument Co. Monocular stimulation was used and the CFF thresholds were determined by continuous decreases in frequency from an initial value of 55 Hz. Background illumination, light intensity of the stimulus, and light/dark ratio were the same for all threshold determinations in both experimental series. After four successive threshold determinations there was a short break, after which an additional four CFF thresholds were measured. The final threshold value was defined as the median of all eight threshold determinations.

All the following performance tests were conducted with the aid of a stimulus-response panel, on which stimuli could be administered and responses recorded electronically. Stimulation was visual, and the subjects responded by touching a switch connected to the respective stimuli. The panel was supplied with 15 stimulus-response units arranged so that they formed three rows and five columns. The switches in the upper two rows were marked clearly with numerals from 0 to 9.

RT Addition (RT = reaction time). In the RT Addition test a series of three stimuli, each lasting 0.4 s and presented at 0.1-s intervals, was displayed on the numbered part of the panel. The subject was asked to add the numbers of the respective stimuli as quickly as possible and indicate the correct answer with the aid of the numbered switches. A total of 36 series were presented, of which the first four were practice series. The sequences for the first 4 and the last 32 series were varied at random from test session to test session. Performance was measured as the mean value of the reaction times for the last 32 series.

Simple RT. Only one of the stimulus-response units on the panel was used for the Simple RT test. The subject was instructed to rest his fingertips lightly on the switch and to respond to a light signal by pressing the switch as quickly as possible. The test consisted of a total

of 176 stimuli, divided into 11 comparable series with 16 consecutive stimuli in each. Each series took about 1 min to perform, and the interval between stimuli varied from 2.5 to 5.0 s. Performance was measured as the median value of the reaction times for the last 160 stimuli. The median value of the reaction times in each time block (1-min period) was also calculated for an analysis of the change in performance over time.

Short-Term Memory. In the Short-Term Memory test a series of stimuli, each lasting 1 s and presented at 1-s intervals, was displayed on the numbered part of the panel. The subject was instructed to reproduce the sequence of numbers presented upon receiving a signal indicating that the sequence was concluded. The answer was given with the aid of the numbered switches. The subject received 10 different series, in which the number of stimuli increased from 4 to 10. The test was used in parallel versions in the different test sessions. The response data were analyzed according to the following two criteria: the number of correctly reproduced stimuli as a percentage of the total number of stimuli (76) and the number of stimuli in the longest completely correct, reproduced series (memory span).

Choice RT. For the measurement of choice reaction time two stimuli, each lasting 0.3 s and presented at 0.01-s intervals, were displayed on the numbered part of the panel. The subject was instructed to decide whether both numbers were odd, both even, or one number odd and one even. The subject answered by touching a switch coded for this purpose on the bottom row. The sequences of the first 6 and the last 72 pairs of stimuli were varied at random from test session to test session. Performance was measured as the mean value of the reaction times for the last 72 pairs of stimuli.

In all trials in both experimental series the tests were given in the following order: (a) Critical Flicker Fusion, (b) Critical Flicker Fusion (after reading or after cycling at 100 W, respectively), (c) RT-Addition, (d) Simple RT, (e) Short-Term Memory, (f) Choice RT, and (g) Critical Flicker Fusion.

RESULTS

Concentration in alveolar air and uptake during exposure

The concentrations of xylene in the samples of alveolar air taken during the experimental conditions in both series are shown in fig. 1. The symbols in the figure represent means of 15 and 8 subjects, respectively. The standard deviations varied between 10—22 % of the respective means. As can be seen from the figure, the increase in alveolar air concentrations

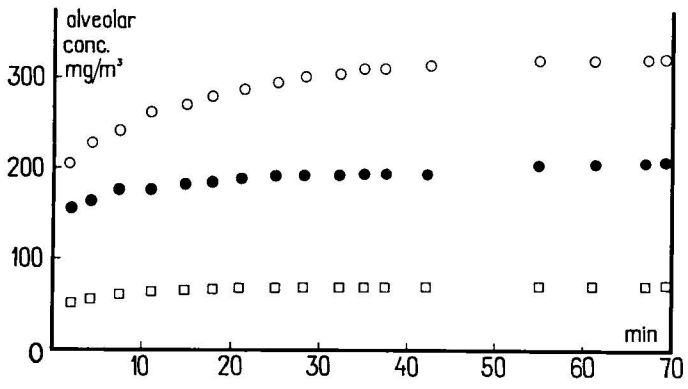

Fig. 1. Mean concentration of xylene in alveolar air. (□ exposure to 435 mg/m³ during rest; ● exposure to 1,300 mg/m³ during rest; ○ exposure to 1,300 mg/m³ during work and rest)

Table 2. Mean and standard deviation of total uptake in milligrams of xylene in experimental series 1 and 2.

Time (min)	Exposure (mg/m^3)					
	435		1,300		1,300 (cycling 100 W)	
	Mean	SD	Mean	SD	Mean	SD
30	78	2.7	234	5.4	870	51.2
70	180	7.6	541	16.3	1,210	83.9

Table 3. Frequency of subjective symptoms after the different trials in series 1 and 2.

Exposure	Symptoms			
	None	Slight	Somewhat	Considerable
Sickness				
Air	14	1	0	0
435 mg/m^3	13	0	2	0
1,300 mg/m^3	10	5	0	0
Air (100 W)	8	0	0	0
1,300 mg/m^3 (100 W)	7	0	1	0
Headache				
Air	11	3	1	0
435 mg/m^3	10	3	2	0
1,300 mg/m^3	7	6	2	0
Air (100 W)	4	3	1	0
1,300 mg/m^3 (100 W)	6	2	0	0
Intoxication				
Air	12	1	1	1
435 mg/m^3	9	5	0	1
1,300 mg/m^3	9	3	3	0
Air (100 W)	7	1	0	0
1,300 mg/m^3 (100 W)	6	1	1	0

occurred mainly at the beginning of the exposure periods when no performance measurements were made. The xylene content in alveolar air was more than 50 % higher in exposure during work at 100 W than in the corresponding exposure during rest. The break in work, which occurred after 30 min of exposure, did not result in any particular change in alveolar air concentration. The increased alveolar air concentration caused by the physical work was thus maintained also during the 40 min of exposure at rest which followed the work period. This finding indicates that the uptake amount of xylene as a percentage of the amount administered is greater under exposure conditions at rest than during the rest period which followed exposure conditions with work.

The mean total uptake of xylene during experimental series 1 and 2 is given in table 2. The total uptake of xylene during the first 30 min of series 2 was calculated as the difference between the total amount of xylene in inspiratory and expiratory air. The uptake during the remaining 40 min of series 2 and the uptake during the two exposure conditions of series 1 was estimated according to a previously described method (2).

Subjective reactions and heart rate during the trials

The results of the interviews carried out after the trials revealed that the menthol "camouflage" had not been entirely successful. Thus 9 of the 15 and 7 of the 8 subjects could distinguish between exposure and nonexposure in the two respective experimental series. In the first series seven of the subjects could furthermore distinguish between the two xylene concentrations.

The extent of the subjective reactions in the two experimental series is shown in table 3. As can be seen from the table, there is a relationship between the exposure conditions and the frequency of subjective symptoms. Most subjects, however, indicated no or negligible subjective symptoms.

The results of the subjects' assessments of their own condition after the trials were analyzed with Friedman's two-way analysis by ranks and the Wilcoxon matched-pairs signed-ranks test (16). The differences between the conditions were slight throughout and did not reach significance. There was however a slight tendency among the subjects to shift their responses closer to the extremes "drowsy," "distracted," and "lazy" after the xylene conditions.

The mean heart rate of the subjects did not vary notably between the conditions with and without exposure to xylene. As a result of the physical work, the subjects carried out the performance tests in the second series with a 10 beats/min higher heart rate on an average than during the previous series. A slight but systematic tendency could also be observed towards a decrease in the individual heart rates during the same trial and between successive trials.

Performance changes during exposure

The results of the first experimental series were analyzed with an analysis of variance model (19), based on a 3×3 Latin square design with repeated measurements (table 1). The model made possible the simultaneous testing of performance changes due to, e.g., different degrees of exposure, repeated measurements (training effect), and the interaction between degree of exposure and training. For CFF and simple RT the variance model was modified to include a test of changes over test trials also. As an additional source of variation in the analysis of the RT test, trend in RT changes over the test period (trend analysis) was introduced, where RT for each time block (1-min period) constituted the values analyzed.

The results from the second experimental series were analyzed with the same variance analysis model after it was adapted for a 2×2 Latin square design with repeated measurements (18, 19).

In the analyses of variance of the results from the first series, no changes in performance as a function of exposure to xylene were found. The differences in performance between the control and experimental conditions were all slight and did not reach significance. Performance on RT Addition and Choice RT improved somewhat with repeated measurements as a result of the training effect [$F(2,24) = 3.28$; $0.05 < p < 0.10$ and $F(2,24) = 3.46$; $p < 0.05$]. CFF was significantly lowered over repeated measurements during the same trial [$F(2,24) = 13.72$; $p < 0.001$], probably as a result of fatigue. As in previous studies on solvents (7, 9), there was a linear decrement in simple RT over time blocks [$F(1,24)$ linear trend $= 26.60$; $p < 0.001$].

The results of the second experimental series revealed an impairment in the subjects' performances on all five tests under exposure to xylene as compared to under control conditions. The greatest differences in performance were found in the following tests: RT Addition [$F(1,6) = 8.58$; $p < 0.05$], Short-Term Memory (memory span) [$F(1,6) = 8.00$; $p < 0.05$], and Choice RT [$F(1,6) = 4.07$; $0.05 < p < 0.10$].

DISCUSSION

The aim of the present study was to examine the extent to which exposure to xylene causes noticeable effects on man's central nervous functions. Since the up-

take of a solvent in the organism varies with the degree of physical work, we have, for previously studied solvents, stated the total uptake at the time when effects on central nervous functions could be established (2).

In the first experimental series the uptake of xylene was estimated at 541 mg with a concentration of 1,300 mg/m^3 in inspiratory air. In the second series, when the exposure period began with a period of physical work, the uptake was estimated at 1,210 mg for the same concentration in inspiratory air. The period of physical work preceding the testing in the second series thus resulted in an obvious increase in uptake. Exposure to 1,300 mg/m^3 in inspiratory air during 70 min of rest did not result in any observable change in the subjects' performance of psychomotor and cognitive tests. However, with the same exposure in inspiratory air, a clear decrement in performance was obtained when uptake was increased through physical work.

This result is clear evidence that the relationship between uptake and effect is of greater relevance in studies on the neurotoxicity of solvents than the relationship between the concentration in inspiratory air and effect. The result thus supports our previously expressed view concerning the need for biological limit values in the evaluation of current TLVs for solvents in inspiratory air.

The biological limit value for xylene with respect to the risk of changes in psychophysiological functions would be found at an uptake of between 600 and 1,000 mg. These values should be directly applicable when the risk of central nervous effects is estimated from exposure periods of around and below 70 min. In estimating the risk of such an effect after exposure to lower concentrations for longer periods of time, one must pay greater attention to metabolism. A great part of the amount of solvent taken up is metabolized already during the period of exposure and should therefore be regarded as biologically inactive (assuming that the metabolites do not themselves exert a neurotoxic effect). For xylene the metabolism appears to be sufficiently rapid to balance partly the increase in total uptake caused by a longer period of exposure (15). The lack of precise information as to the rate of metabolism of xylene means that the risk of a central nervous effect cannot, however, be excluded after, e.g., 8 h of exposure to concentrations around the TLV (435 mg/m^3).

It can furthermore not be excluded that a concentration of xylene around the TLV can cause subjective symptoms in many exposed workers. The relationship between exposure and subjective symptoms was rather slight in the present study. However, the exposure methods used, with breathing valve, mouthpiece and noseclip and also menthol camouflage of the smell and taste of the solvent, obstructed the occurrence of certain subjective symptoms such as irritation of the eyes and nose (6, 12).

In the present study the greatest differences in performance between exposure and control conditions were measured in the more complex and cognitive tests of the test battery. The simpler psychomotor and perceptual tests, which in previous studies have revealed effects more effectively than other types of tests, revealed only slight changes in performance in this case. On the assumption that this reversal in the relative sensitivity of the tests is not random and only apparent, it is reasonable to assume that there is some connection with the fact that the present study included a period of physical work, which affected the arousal of the subjects at the time of testing. Heart rate at the time of testing after physical work was increased by 10 beats/min on an average when compared to the corresponding experimental conditions at rest. There are several examples in the literature of how an induced increase in arousal can result in improved performance on simple psychomotor and perceptual tests, while no improvement or even decrement in more complex cognitive tests is seen (4, 5, 17). The explanation given for these changes in performance is that the optimal level of arousal varies for different types of mental tasks. Our hypothetical explanation is therefore that the physical work raised the degree of arousal to a more optimal level for simple psychomotor and perceptual tasks, and thus rendered performance capability on these tasks more resistant to the depressant effect of exposure to the solvent. A

test of this hypothesis would be desirable, since it has implications for the interpretation of effects. A confirmation of this hypothesis could lead to the definition and the assessment of two biological limit values, one based on a depressant narcotic action affecting, e.g., attention and vigilance functions and another based on a more general influence on intellectual functions.

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