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Decrease of Inhaled Toluene, Ethyl Benzene, m-Xylene, or Mesitylene in Rat Blood after Combined Exposure to Ethyl Acetate

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Various kinds of solvent mixtures are used in the manufacture and application of paints, lacquers, printing inks, or glues. These mixtures frequently contain aromatic compounds such as toluene, ethyl benzene, m-xylene, or mesitylene (1,3,5-methyl benzene) in combination with esters such as ethyl acetate. These solvent compositions may be absorbed by humans during exposure at work. Toxicokinetic interactions between aromates and esters can be expected because of the partially common pathway of biotransformation. The aim of the present investigations in rats was to clarify whether the blood concentration of inhaled toluene, ethyl benzene, m-xylene or mesitylene can change after the concomitant pulmonary absorption of ethyl acetate. The results should yield informations relevant for the assessment of health risk at worksite situations.

MATERIALS AND METHODS

Ethyl acetate, toluene, and m-xylene were purchased from Merck - Darmstadt/FRG, mesitylene from Baker - Deventer/Holland, all of analytical grade. Adult female SPF Sprague-Dawley rats, weighing 200 - 220 g were obtained from the Central Breeding Station of the University of Heidelberg/FRG. The animals were housed under conditions as described elsewhere (Römer et al. 1985). Groups of 5 rats each - mixed randomly - were exposed in a 20 l glass chamber under dynamic conditions (air flow 1.25 l/min) for 2 h to various concentrations of the aromates without or in combination with two different concentrations of ethyl acetate in air. Atmospheres containing the aromates and ethyl acetate fluctuated no more than $\pm$ 5 percent and were delivered by means of a specially constructed evaporator. Exposure concentrations during the inhalations were monitored repeatedly. During the exposures food and water were withdrawn. Immediately after the inhalation blood (0.02 ml) was collected for analysis from the retro-orbital plexus of the rats using disposable pipettes. The air concentrations of the solvents and the blood concentrations of the aromates were determined by gas chromatography using methods described in detail previously (Römer et al. 1986). The means $\pm$ SEM were calculated from the corresponding individual values

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determined. The treatment groups were compared with controls by statistical analysis using Dunnett's (1955) test. The level of significance chosen was a p below 0.05.

RESULTS AND DISCUSSION

The threshold limit values (ACGIH 1988; DFG 1988) amount to 100 ppm for toluene, ethyl benzene, and m-xylene, or 400 ppm for ethyl acetate, referring to an 8-h work shift. No hygienic limit value is assigned for mesitylene. The lower 2-h exposure levels applied in the present study are in the same order as these threshold limit values and are therefore of practical relevancy. The higher solvent concentrations used in the present investigations are applied to simulate the possible situation of intoxications and to elucidate the relationship between dose and blood concentration. The co-exposure with ethyl acetate lowered the blood concentrations of inhaled toluene, ethyl benzene, m-xylene or mesitylene (Table 1 - 4). This reduction was statistically significant following a 2-h exposure to 230 ppm toluene in combination with 1000 ppm ethyl acetate (Table 1), 650 ppm ethyl benzene with 1000 ppm ethyl acetate (Table 2) or 100 ppm m-xylene with 4000 ppm ethyl acetate (Table 3). A similiar significant diminution of the blood level of the aromates by ethyl acetate co-inhalation (1000 or 4000 ppm) was observed following higher exposure concentrations of toluene (Table 1) or m-xylene (Table 3). We have no satisfactory explanation why ethyl acetate co-administration lowers the blood content of the inhaled aromates. The underlying mechanism should be clarified in further experiments. A metabolic interaction, e.g. enhanced disposition of the aromates, seems to be the source of the effects observed. On the other hand the solubility of the solvents (partition

Table 1. Blood concentrations (means $\pm$ SEM from 5 rats per group) of toluene after 2-h inhalation without or in combination with ethyl acetate.

Exposure concentration (ppm)		Blood concentration Toluene (10^{-6} mol/l)
Toluene	Ethyl acetate	
140	0	22.0 $\pm$ 3.3
140	1000	15.5 $\pm$ 1.3 (-29.5 %)
140	4000	15.3 $\pm$ 1.1 (-30.5 %)
230	0	49.9 $\pm$ 6.0
230	1000	31.4 $\pm$ 2.9 (-37.1 %) (a)
230	4000	26.8 $\pm$ 2.6 (-46.3 %) (a)
420	0	154.7 $\pm$ 18.0
420	1000	103.8 $\pm$ 15.6 (-32.9 %) (a)
420	4000	100.0 $\pm$ 7.4 (-35.4 %) (a)
690	0	234.3 $\pm$ 8.2
690	1000	190.9 $\pm$ 5.8 (-18.5 %) (a)
690	4000	168.3 $\pm$ 5.1 (-28.2 %) (a)

Decrease (in percent) in parenthesis. - (a) significant: p less than 0.05 .

coefficients for lipoprotein/water) could be altered by the presence of ethyl acetate. This should be elucidated. In view of the assessment of the health risk it can be concluded from the results obtained that co-

Table 2. Blood concentrations (means ± SEM from 5 rats per group) of ethyl benzene after 2-h inhalation without or in combination with ethyl acetate.

Exposure concentration (ppm)		Blood concentration Ethyl benzene (10^{-6} mol/l)
Ethyl benzene	Ethyl acetate	
120	0	22.5 ± 1.5
120	1000	22.4 ± 2.2 (-0.4 %)
120	4000	19.0 ± 1.0 (-15.6 %)
240	0	68.7 ± 8.4
240	1000	66.1 ± 3.6 (-3.8 %)
240	4000	50.3 ± 3.6 (-26.8 %)
350	0	104.5 ± 6.0
350	1000	90.1 ± 14.8 (-13.8 %)
350	4000	90.2 ± 10.6 (-13.7 %)
650	0	260.7 ± 12.4
650	1000	194.3 ± 12.8 (-25.5 %) (a)
650	4000	192.7 ± 14.1 (-26.1 %) (a)

Decrease (in percent) in parenthesis. - (a) significant: p less than 0.05 .

Table 3. Blood concentrations (means ± SEM from 5 rats per group) of m-xylene after 2-h inhalation without or in combination with ethyl acetate.

Exposure concentration (ppm)		Blood concentration m-Xylene (10^{-6} mol/l)
m-Xylene	Ethyl acetate	
100	0	17.5 ± 1.7
100	1000	14.6 ± 1.3 (-16.6 %)
100	4000	11.2 ± 1.7 (-36.0 %) (a)
200	0	68.1 ± 13.4
200	1000	66.5 ± 8.9 (-2.3 %)
200	4000	50.8 ± 4.1 (-25.4 %)
340	0	115.1 ± 10.4
340	1000	87.3 ± 4.5 (-24.2 %) (a)
340	4000	84.1 ± 6.1 (-26.9 %) (a)
560	0	231.6 ± 15.4
560	1000	191.1 ± 13.3 (-17.5 %)
560	4000	163.0 ± 11.6 (-29.6 %) (a)

Decrease (in percent) in parenthesis. - (a) significant: p less than 0.05 .

Table 4. Blood concentrations (means ± SEM from 5 rats per group) of mesitylene after 2-h inhalation without or in combination with ethyl acetate.

Exposure concentration (ppm)		Blood concentration Mesitylene (10^{-6} mol/l)
Mesitylene	Ethyl acetate	
120	0	15.7 ± 2.2
120	1000	15.1 ± 1.7 (-3.8 %)
120	4000	13.9 ± 1.5 (-11.5 %)
180	0	19.6 ± 3.2
180	1000	19.3 ± 1.1 (-1.5 %)
180	4000	18.8 ± 0.8 (-4.1 %)
400	0	75.8 ± 2.1
400	1000	75.2 ± 6.4 (-0.8 %)
400	4000	68.8 ± 7.8 (-9.2 %)
720	0	143.5 ± 4.3
720	1000	141.1 ± 10.4 (-9.8 %)
720	4000	118.4 ± 5.9 (-17.5 %)

Decrease (in percent) in parenthesis. - p more than 0.05 .

exposures to concentrations in the order of the threshold limit values, e.g. 100 ppm of toluene, ethyl benzene, m-xylene or mesitylene, with 400 ppm of ethyl acetate should not be followed by a dangerous change of the blood levels of the aromates.

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