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Kinetics and metabolism.**

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Coexposure of man to *m*-xylene and methyl ethyl ketone

Kinetics and metabolism

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LIIRA J, RIIHIMÄKI V, ENGSTRÖM K, PFÄFFLI P. Coexposure of man to *m*-xylene and methyl ethyl ketone: Kinetics and metabolism. *Scand J Work Environ Health* 14 (1988) 322–327. In a study of the kinetics and metabolic interaction of xylene and methyl ethyl ketone (MEK) eight male volunteers were exposed to *m*-xylene (100 ppm) and MEK (200 ppm). The exposures to the two compounds were carried out both separately and in combination. Respiratory uptake and blood concentration, as well as urinary metabolites (methyl hippuric acid and 2,3-butanediol), were monitored. Coexposure to xylene and MEK resulted in inhibited xylene metabolism. The xylene concentration in blood increased significantly, and the urinary excretion of methyl hippuric acid decreased. The combined exposure did not cause any change in the concentration of MEK in the blood or the excretion of 2,3-butanediol in the urine. Exposure to MEK 20 h before the *m*-xylene exposure had no detectable effect on the kinetics of *m*-xylene.

Key terms: human exposure, xylene.

Ketone solvents are well known for their ability to potentiate the intrinsic toxicities of other solvents. Ketone pretreatment enhances the nephrotoxicity and hepatotoxicity of halogenated hydrocarbons (3). Potentiation is maximal if ketone administration precedes that of the halogenated hydrocarbon by about 16 h (5, 6, 22). On the other hand ketones, eg, methyl ethyl ketone (MEK), appear to interfere with the metabolism of *n*-hexane and methyl *n*-butyl ketone, the result being an increase in the neurotoxicity of these solvents (1, 19, 21).

The metabolism of MEK has been studied in experimental animals (4, 7). MEK is metabolized to 2-butanol, 3-hydroxy-2-butanone, and 2,3-butanediol, the last of which seems to be the end metabolite (4, 7). Only small amounts, about 0.1 % of the total uptake, are excreted in the urine of man as MEK (14) and 3-hydroxy-2-butanone (15).

Absorbed xylene is extensively metabolized and excreted as methyl hippuric acid in the urine (2, 16). The metabolism of xylene is inhibited by oral doses of ethanol (17). Studies of combined inhalation exposure to moderate concentrations of *m*-xylene and ethylbenzene indicate that these aromatic solvents inhibit each other's metabolism (8, 10). However, *m*-xylene and 1,1,1-trichloroethylene do not seem to interact (20).

In order to study ketone-aromatic metabolic interactions, we exposed volunteers to MEK and *m*-xylene in a dynamic exposure chamber. The potential effect

of preexposure to MEK on xylene metabolism was also considered.

Subjects and methods

The test subjects were eight healthy male university students who volunteered for the study. Their ages ranged between 22 and 31 (mean 25.5) years, their weights between 57 and 87 (mean 73.0) kg, and their heights between 169 and 194 (mean 182.1) cm. Their mean minute ventilation during sedentary activity was estimated to be approximately 11 l/min on the basis of previous measurements involving similar subjects and identical conditions (16). The subjects gave their informed consent, and the principles of the Declaration of Helsinki concerning human medical studies (26) were strictly followed. The study design was approved by the ethical committee of the Finnish Institute of Occupational Health. A clinical examination of the volunteers before and after the study disclosed no abnormal findings.

The exposures were carried out in a dynamic flow exposure chamber as described in an earlier study (16). Analytical grades of MEK and *m*-xylene (Merck-Schuchard, Darmstadt, Federal Republic of Germany) were used.

The eight subjects, divided into two groups, were exposed for 4 h daily while in a sedentary state. The exposures were scheduled at intervals of at least one week, except for the week when the exposures (MEK preceding xylene) took place on successive days. The series of four exposures consisted of one separate exposure to MEK and two separate xylene exposures and one combined exposure. The target concentration was 8.2 mmol/m³ (200 ppm) for MEK and 4.1 mmol/m³ (100 ppm) for *m*-xylene. According to continuous

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monitoring of the solvent concentration in the chamber, the observed mean concentration was 200.1 (SD 3.6) ppm for MEK and 100 (SD 3.3) ppm for *m*-xylene.

Samples of venous blood, expired air, and urine were collected during and after the exposures as follows. Venous blood was obtained through a teflon infusion needle inserted into a large forearm vein. The exhaled air samples were collected with a two-way respirator mouthpiece (dead-space volume 70 ml) into polyester laminated aluminum-foil bags with a 4-l capacity. A clip was used to prevent breathing through the nose. The blood samples were collected at 1-h intervals during the exposures and for a period of 210 min after the exposures, and the expired air samples were collected until the next morning. Urine samples were obtained at 2-h intervals during the exposure day, and the subjects were requested to collect all urine voided in separate samples until the next morning.

Analysis of the samples

The MEK and *m*-xylene concentrations in whole venous blood were analyzed by gas chromatography (Hewlett-Packard 5750) using the headspace technique. A flame-ionization detector and a packed column (internal diameter 4 mm, length 2 m, 10 % of OV 17 on acid-washed Chromosorb W) were applied. A glass serum vial containing 1 ml of venous blood was sealed with a teflon-covered rubber plug and stored at 60°C for 30 min before the sampling. The peak heights were compared to a calibration curve plotted when the blood concentrations of *m*-xylene and MEK were known.

The MEK and *m*-xylene concentrations of the exhaled air were analyzed by gas chromatography (Hewlett-Packard 5750) using a packed column (OV-17, length 1 m). A gas-tight syringe (100 ml) was used to draw air samples through the bag wall, the air then being injected into the chromatograph via a gas sampling valve (loop volume 5 ml). The analyses were made at room temperature. The peak heights were compared to calibration curves plotted when the concentrations of MEK and *m*-xylene were known.

The concentrations of 2,3-butanediol in urine were analyzed with a modification of the derivation method by Robinson & Reive (18). 2,3-Butanediol (Fluka AG, Buchs, Switzerland) was extracted and derivatized with *n*-butyl boronic acid (Pierce, Rockford, Illinois, United States); 1 ml of urine was mixed with 1 ml of acetonitrile and salted with 200 mg of sodium chloride; the sample was shaken and left standing for 30 min; and equal amounts of supernatant (250 µl) and 1-butyl boronic acid (10 mg/ml of acetone) were shaken in a tube. One microliter of the derivatized sample was injected into a capillary gas chromatograph (Hewlett-Packard 5890, capillary column OV 101, length 12 m, internal diameter 0.2 mm, equipped with a flame-ionization detector). The 2,3-butanediol isomers were separated into two peaks in a chromatogram (*d* and *l* forms and the meso form); in the calculations the two peaks

were added together. Duplicate samples were analyzed at the same time and compared with standards of known amounts of 2,3-butanediol. The lowest detectable 2,3-butanediol concentration in urine was 20 µmol/l, and the recovery of the 2,3-butanediol in urine was 31 %. The coefficient of variation at the concentration of 100 µmol/l was 0.18. Neither acid nor base hydrolysis nor the use of beta-glucuronidase increased the yield of the 2,3-butanediol obtained from the urine samples.

Urinary *m*-methyl hippuric acid was analyzed by gas chromatography as described previously (9).

Kinetic calculations

Pulmonary retention (*R*, % of exposure concentration) was calculated according to the formula $R = (C_{\text{exp}} - C_{\text{exh}}) / C_{\text{exp}} \times 100$, where C_{exp} = exposure or the inhaled solvent concentration (µmol/l) and C_{exh} = solvent concentration in the normally expired air samples (µmol/l). The total pulmonary uptake (U_t , mmol) was calculated by the formula $U_t = (C_{\text{exp}} - C_{\text{exh}}) \times V \times t$, where V = minute ventilation (l/min) and t = duration of exposure (min).

The apparent clearance (Cl_{app}) was calculated with the formula $Cl_{\text{app}} = U_t / \text{AUC}$, where AUC = the area under the blood concentration-time curve. The AUC was determined on the basis of the trapezoidal rule during the exposure and during the monitored elimination phase. The residual elimination was estimated from the slow phase elimination rate constants reported in earlier studies (16). For xylene the estimated elimination rate constant for 3 to 16 h after exposure was $k_2 = 0.0015$ (half-time = 7.7 h), and from 16 h onwards it was $k_3 = 0.00067$ (half-time = 17.3 h) (16). For MEK the slope of the beta phase of elimination (60 to 210 min after exposure) was resolved from a linear regression line determined by the least squares method in a semilogarithmic presentation of the blood concentration-time plot. The calculated beta-phase elimination rate constant (k) for MEK was $k_2 = 0.007$ (half-time = 1.6 h). From 210 min onwards, the MEK AUC_{bl} was resolved on the assumption that the determined beta-phase elimination rate constant was the terminal one.

The trapezoidal rule was used to calculate the pulmonary elimination from the expired air concentration-time plot. In the slow phase of elimination (from 210 min onwards), the beta-phase elimination rate constants were used as for the calculation of the AUC.

Student's *t*-test for paired samples was used for the statistical analyses.

Results

The pulmonary retention of both solvents remained relatively constant under all conditions of exposure. The retention of MEK throughout the 4-h exposures was about 41 to 45 %, that of xylene being about 56

Table 1. Pulmonary retention and estimated total pulmonary uptake during the exposure to 100 ppm of *m*-xylene (xylene a) and 200 ppm of methyl ethyl ketone (MEK) and in coexposure to the same concentrations of both solvents. *m*-Xylene exposure (100 ppm) with a preceding MEK exposure (200 ppm, one day before) is also depicted (xylene b).

Exposure conditions	Pulmonary retention (%)				Total pulmonary uptake (mmol)			
	Xylene		MEK		Xylene		MEK	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Xylene a	57.4	6.1	-	-	6.2	0.7	-	-
Xylene b	58.6	7.6	-	-	6.3	0.7	-	-
Xylene + MEK	56.1	7.6	-	-	6.0	0.8	-	-
MEK	-	-	41.1	7.1	-	-	8.9	1.5
MEK + xylene	-	-	44.6	7.6	-	-	9.6	1.6

Figure 1. Methyl ethyl ketone (MEK) concentration ($\mu\text{mol/l}$) (mean and SD) in venous blood during and after an inhalation exposure to 200 ppm of MEK alone (open circles) and together with 100 ppm of *m*-xylene (closed circles).

Figure 2. *m*-Xylene concentration ($\mu\text{mol/l}$) (mean and SD) in venous blood during and after exposure to 100 ppm of *m*-xylene alone (open circles) and together with 200 ppm of methyl ethyl ketone (closed circles).

to 59 %. The combination exposure had no significant effect on the total pulmonary uptake of xylene or MEK (table 1).

The concentration of MEK in blood increased rapidly during the first hour of exposure, after which a slow-

er but steady increase took place (figure 1). After exposure there was a slightly faster elimination phase that lasted for the first 30 min, after which the rate of elimination was apparently constant (figure 1). The calculated slow-phase elimination half-time was 95 min ($k_{el\beta} = 0.007\text{ min}^{-1}$). Coexposure had no marked effect on the concentration of MEK in blood during and after exposure (figure 1).

The concentration of xylene in blood increased in a manner similar to MEK throughout the 4-h exposure, though the absolute concentration in blood was nearly one order of magnitude lower owing to the lower level of exposure, the lower solubility of xylene in blood, and the efficient metabolism of xylene. A typical multiphasic elimination curve was detected after the exposure (figure 2). Coexposure to xylene and MEK caused the xylene concentration in blood to increase nearly twofold as compared with the xylene concentration in blood following exposure to xylene alone. This increase was also noted throughout the 210-min elimination phase (figure 2).

Concomitant xylene and MEK exposure significantly reduced the apparent clearance of xylene, whereas the apparent clearance of MEK remained unchanged (table 2). These findings suggest that MEK had an inhibitory effect on xylene metabolism. Conversely, there was no clear indication of an overall metabolic alteration for MEK.

The pulmonary excretion of solvents was followed until the next morning. In the elimination phase, the solvent concentration in expired air is dependent on the solvent concentration in mixed venous blood and the blood/air distribution coefficient of the solvent in question. The estimated pulmonary elimination of xylene was 8.4 to 10.5 % of the total uptake, and the corresponding values for MEK were 3.2 to 3.4 %. Coexposure did not affect the pulmonary excretion (table 3). Most of both solvents was metabolized in the body, the primary metabolite of xylene being methyl hippuric acid. 2,3-Butanediol has previously been found in urine following experimental exposure to MEK, but only a small proportion (about 3 %) of the total MEK dose is excreted as 2,3-butanediol in the urine (13). The total amounts of methyl hippuric acid

and 2,3-butanediol excreted within 24 h of the beginning of the exposure are shown in table 3.

The excretion of methyl hippuric acid was significantly reduced during the combined exposure. The difference diminished during the 4 h after exposure apparently because of the withdrawal of the metabolic inhibition by MEK concomitant with decreasing solvent concentrations in the blood. No compensatory excess of MHA excretion was detected in the postexposure phase (figure 3).

The excretion of 2,3-butanediol in urine showed a very large interindividual variation. The 24-h excretion of 2,3-butanediol was more than one order of magnitude less than the excretion of methyl hippuric acid (table 3) and only a minor percentage (about 2–3 %) of the absorbed MEK was excreted in the urine in the form of 2,3-butanediol. Significantly greater excretion rates of urinary 2,3-butanediol were detected in the afternoon following the combined exposure (figure 4), and the difference in the total amount excreted was nearly significant (table 3). It must be noted, however, that, in comparison to earlier observations under identical conditions (13), the

2,3-butanediol excretion detected in this study after exposure to MEK alone was exceptionally low.

The amount of methyl hippuric acid excreted during a 24-h period represented 71.4 to 80.3 % of the estimated xylene pulmonary uptake (60.7 % in coexposure), whereas the 2,3-butanediol excretion represented only 1.7 to 3.9 % of the MEK uptake. It is

Table 2. Apparent clearance of *m*-xylene and methyl ethyl ketone (MEK) in different exposures. (For the exposures see table 1.)

Exposure conditions	Apparent clearance (l/min)			
	Xylene		MEK	
	Mean	SD	Mean	SD
Xylene a	1.68	0.39	·	·
Xylene b	1.66	0.33	·	·
Xylene + MEK	0.87	0.22*	·	·
MEK	·	·	0.32	0.11
MEK + xylene	·	·	0.38	0.23

* $P < 0.01$ (when compared to xylene a exposure).

Table 3. Pulmonary elimination of *m*-xylene and methyl ethyl ketone (MEK), as well as urinary methyl hippuric acid (MHA) and 2,3-butanediol (2,3-BD) excretion, over 20 h after exposure according to the different exposure modes. (For the exposures see table 1.)

Exposure conditions	Pulmonary elimination (mmol)				Urinary excretion (mmol)			
	Xylene		MEK		MHA		2,3-BD	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Xylene a	0.61	0.10	·	·	4.94	0.63	·	·
Xylene b	0.53	0.13	·	·	4.50	0.35	·	·
Xylene + MEK	0.64	0.16	·	·	3.64	0.48*	·	·
MEK	·	·	0.29	0.15	·	·	0.16	0.07
MEK + xylene	·	·	0.32	0.08	·	·	0.33	0.20

* $P < 0.01$ (when compared with xylene a exposure).

Figure 3. Methyl hippuric acid excretion ($\mu\text{mol/h}$) (mean and SD) in urine during and after exposure to 100 ppm of *m*-xylene alone (open circles) and together with 200 ppm of methyl ethyl ketone (closed circles).

Figure 4. 2,3-Butanediol excretion ($\mu\text{mol/h}$) (mean and SD) in urine during and after exposure to 200 ppm of methyl ethyl ketone alone (open circles) and together with 100 ppm of *m*-xylene (closed circles).

reasonable to assume that the reduced excretion of methyl hippuric acid that occurred with a concomitant elevation of the xylene concentration in blood indicates that, in man, coexposure to xylene and MEK results in inhibited xylene metabolism, the inhibition being caused by MEK. It is interesting to note that, whereas coexposure significantly reduced the methyl hippuric acid excretion over a 24-h period, there was only a barely detectable tendency towards a corresponding increase in the pulmonary excretion of unchanged xylene. Reduced metabolic clearance of a lipid-soluble compound could lead to enhanced distribution to storage sites, ie, fat tissues, but there was no evidence of a marked effect, as the xylene concentrations in the blood after the combined exposure were not elevated in the 16-h postexposure samples. A shift in the involvement of the major metabolic pathways of xylene, ie, side-chain oxidation versus ring oxidation, could also be possible, but this possibility was not investigated.

Discussion

In this study the observed pulmonary retention of *m*-xylene was 56 to 59 %. This amount is nearly the same as that of an earlier study (about 60 %) (16). The retention of MEK in this study, 41 to 45 %, was somewhat lower than our earlier observation (53 %) (13). The observed decrease in the retention of MEK may largely be an artifact caused by variations in breathing techniques, eg, hyperventilation with a proportional increase in deadspace air.

The combined exposure seemed to have no significant effect on the pulmonary uptake of either solvent, although the pulmonary uptake of xylene tended to be marginally lower in the joint exposure.

The equal uptake during combined exposure is compatible with the ventilation dependency of the pulmonary uptake of solvents having a high solubility in blood and tissues. Although the combined exposure reduced the metabolic clearance of xylene, tissue uptake nevertheless continued efficiently.

Xylene undergoes microsomal transformation to methyl benzyl alcohol, which is further converted to methyl benzoic acid by cytosolic alcohol and aldehyde dehydrogenases (2). MEK is transformed by carbon chain ω -1 hydroxylation to 3-hydroxy-2-butanone and is subsequently reduced to 2,3-butanediol (4, 7). The first step of MEK metabolism is probably catalyzed by the microsomal monooxygenase system (4).

Our observation that MEK clearly increased the xylene concentration in blood indicates that MEK probably interacts with the initial monooxygenase-catalyzed step of biotransformation. This phenomenon is accompanied by a corresponding reduction in the formation and excretion of methyl hippuric acid. Whether or not other enzymatic steps are affected cannot be concluded from the present data. The biotransformation of MEK

seems to be undisturbed by the presence of xylene although it was of interest to note that in the combined exposure the urinary 2,3-butanediol excretion was higher later in the afternoon, and the postexposure blood MEK concentration tended to be lower than in the exposure to MEK alone. Nevertheless, we hesitate to conclude that the increased urinary excretion of 2,3-butanediol truly represents an interaction caused by *m*-xylene in the joint exposure.

In a Swedish study on combined inhalation exposure involving human volunteers, acetone (about 500 ppm) did not affect the metabolism of styrene (about 70 ppm, 2 h) (25). Large intraperitoneal doses of acetone did not affect the excretion of styrene metabolites in rats either (12). Acetone induces aniline *p*-hydroxylase and ethoxycoumarin *O*-deethylase enzyme activities in rats (23, 24). These enzymes are similarly induced by the administration of ethanol, and both acetone and ethanol are called ethanol-type inducers of microsomal oxidation. In our studies performed on rats, the oral administration of MEK (1.2 g/kg on three consecutive days) caused a phenobarbital-type cytochrome P-450 enzyme induction (unpublished data). The different induction patterns may reflect the differences between these two ketones as to their primary metabolic routes. MEK may compete with xylene for the same microsomal enzymatic site of metabolism, whereas acetone and styrene seem to be metabolized by separate routes of microsomal oxidation.

In animal studies, the hepatotoxicity of chlorinated hydrocarbons was potentiated by relatively high doses of MEK (about 1–2 g/kg, administered orally) given to the test animals about 16 h before carbon tetrachloride (5, 6, 22). The biochemical mechanism by which ketone pretreatment potentiates the hepatotoxicity of carbon tetrachloride is still not clear and may be at least partly based on mechanisms other than the induction of microsomal oxidative enzymes.

In our study, a preceding inhalation exposure to MEK failed to cause any significant changes in xylene kinetics and metabolism. However, as the estimated xylene clearance nearly equals the liver blood flow (1.50 l/min) (11), it is not surprising that we detected no increase in the metabolic rate of xylene. Enhanced xylene metabolism in extrahepatic tissues is possible, but in this study we found no evidence of an increased total metabolic capacity.

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