

Kinetics of m-xylene in man

Influence of intermittent physical exercise and changing environmental concentrations on kinetics

by VESA RIIHIMÄKI, M.D., M.Sc., PIRKKO PFÄFFLI, M.Sc., and
KAI SAVOLAINEN, M.D.

RIIHIMÄKI, V., PFÄFFLI, P. and SAVOLAINEN, K. Kinetics of m-xylene in man: Influence of intermittent physical exercise and changing environmental concentrations on kinetics. *Scand. j. work environ. & health* 5 (1979) 232–248. Volunteer subjects were exposed to m-xylene 6 h/d over five successive days under the following types of environmental conditions: exposure type I: constant xylene concentration in air, subjects performed periodic ergometer exercise at 100 W; exposure type II: varying xylene concentration in air with peak levels coinciding with periodic ergometer exercise; and exposure type III: constant xylene concentration in air, subjects sedentary. The three types of exposure were identical in that the time-weighted averages of the xylene concentrations in the air inhaled over the whole day were about the same (in most cases 4.1 mmol/m³). Nevertheless, the daily xylene uptakes proved to be somewhat different, while the maximum rates of xylene uptake occurring in the three exposure types were markedly different. In exposure types I and II the main part of the day's xylene uptake took place during the repeated short exercise sessions and resulted, partly due to an altered distribution of organ blood flow, in a greater distribution of xylene to tissues with slow elimination characteristics (and a greater cumulation of xylene) than in exposure type III. Although relatively high pulmonary uptake rates of xylene (about 150–300 μ mol/min) were estimated to have occurred over 15-min periods at a time, no signs of saturation kinetics were noted. The relative contributions of the two biotransformation pathways of m-xylene (side-chain oxidation and aromatic oxidation) were not markedly altered by the different environmental conditions, but aromatic oxidation, producing 2,4-xyleneol, tended to increase slightly over the five exposure days. The blood xylene levels attained under stable near-equilibrium conditions and under conditions of greatly increased uptake appeared to be directly related to the rate of xylene uptake, whereas no such relation existed in the phase of decreasing xylene uptake.

Key words: human exposure, kinetics, m-xylene, physical exercise.

The significance of physical exercise on solvent uptake was first pointed out by Zenz and Berg (27), and more recently

several investigators have studied solvent kinetics under conditions of varying degrees and durations of exercise (1, 2, 8, 15, 16, 17). Some theoretical aspects of the influence of physical work load on the retention and metabolism of solvents with different pharmacokinetic characteristics have been discussed by Droz and Fernandez (11). It is now appreciated that the increased pulmonary ventilation caused by

¹ Department of Industrial Hygiene and Toxicology, Institute of Occupational Health, Helsinki, Finland.

Reprint requests to: Dr. Vesa Riihimäki, Institute of Occupational Health, Haartmaninkatu 1, SF-00290 Helsinki 29, Finland.

physical exercise (in heavy work up to six to seven times that of the resting state) carries increased quantities of solvent vapor to the pulmonary alveolar space in a unit time and that the absorption of the solvent will depend on its solubility in the blood and tissues, as well as on the efficiency of its biotransformation in the body. Thus, for solvents highly soluble in blood and tissues and efficiently metabolized, a rise in pulmonary ventilation may be followed by a nearly parallel increase in pulmonary uptake (11). Less attention has been paid to other physiological exercise-induced changes such as alterations in the distribution of blood flow.

A comprehensive study on toluene was recently performed by Veulemans and Masschelein (24, 25, 26) to elucidate the effects of different exposure patterns and different degrees of physical activity on kinetics. We have also investigated the kinetics of m-xylene in human volunteers under conditions which would simulate occupational exposures involving five

daily exposures to stable or periodically varying m-xylene concentrations in the air during sedentary activity or rest combined with intermittent physical exercise.

MATERIAL AND METHODS

Subjects

The subjects were 18 healthy male volunteers, 18–35 years of age. The study was conducted with strict adherence to the principles of the Declaration of Helsinki adopted by the World Medical Association (28). No abnormal findings were disclosed in a routine clinical examination (erythrocyte sedimentation rate, hematology, serum glutamate-oxalacetate transaminase, serum glutamate-pyruvate transaminase, serum creatinine, urinary albumin, glucose,

Table 1. Some anthropometric and physiological characteristics of the subjects.

Person	Age (years)	Skin surface area (m ²)	Weight (kg)	Ventilation at basal conditions, table values (l/min)	Ventilation at 100 W exercise, in the laboratory (l/min)
<i>Exposure type I^a</i>					
H.R.	26	1.99	78	7.2	38
P.K.	23	2.09	80	7.5	40
E.M.	26	1.91	75	6.9	38
H.L.	23	2.10	82	7.6	38
<i>Exposure type II</i>					
M.N. ^b	18	1.81	71	6.5	38
J.P.	22	1.67	56	6.0	42
V.R. ^b	35	1.90	70	6.8	35
K.S.	27	2.00	79	7.2	34
H.R.	26	1.99	78	7.2	38
A.L.	20	1.77	63	6.4	37
V-M.A.	21	1.90	70	6.8	42
P.L.	22	1.92	75	6.9	38
<i>Exposure type III</i>					
E.I.	21	1.82	68	6.6	32
P.S.	24	1.78	65	6.4	37
H.M.	28	1.79	67	6.4	36
E.Ö.	22	1.95	68	7.0	30
K.L.	23	2.00	77	7.2	37
D.K.	22	1.94	74	7.0	32

^a Group also includes the first four subjects listed under exposure type II.

^b Model person for the determination of mean ventilation.

and sediment). Lung function (spirometry, capnography and transfer factor) and cardiac function (electrocardiography at rest and during submaximal ergometer exercise) were normal. Electroencephalography did not reveal any significant deviations from normal. Clinical chemical investigations were repeated after the exposure period, and no significant changes were noted. Some anthropometric and physiological characteristics of the subjects are presented in table 1.

Exposure

The exposures were carried out in a dynamic controlled-environment exposure chamber, the technical features of which have been described previously (20). Four or six subjects at a time were exposed to m-xylene (laboratory grade, Merck, Darmstadt, Federal Republic of Germany) in the chamber over five successive days, 3 h in the morning and 3 h in the afternoon with a 1-h lunch break in between. Three dif-

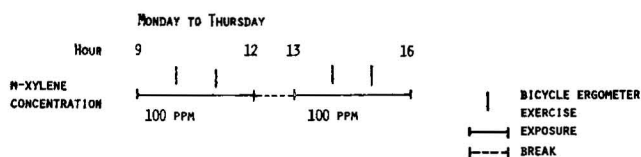


Fig. 1. Exposure type I: Constant concentration of m-xylene in the air of the chamber. Subjects exercised on a bicycle ergometer at 100 W for 10 min four times per day.

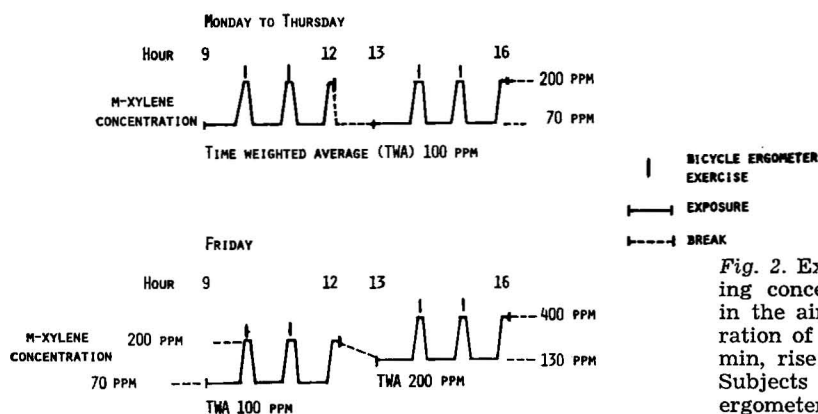


Fig. 2. Exposure type II: Varying concentration of m-xylene in the air of the chamber. Duration of peak concentration 10 min, rise and fall 5 min each. Subjects exercised on a bicycle ergometer at 100 W for 10 min four times per day.

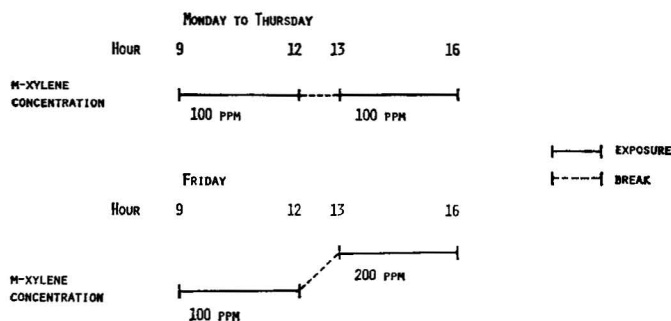


Fig. 3. Exposure type III: Subjects were sedentary throughout the experiment.

Table 2. Concentration of m-xylene in chamber air during the different types of exposure. Mean values and ranges (in parentheses) are given.

Exposure	Number of days	Xylene concentration (ppm v/v)	
		Constant concentration	TWA ^a of varying concentration
Type I			
Monday—Thursday	8	90 (87—93)	
Friday			
Morning	2	89	
Afternoon	2	191 (188—193)	
Type II			
Monday—Thursday	8		93 (91—99)
Friday			
Morning	2		89 (87—91)
Afternoon	2		187 (175—199)
Type III			
Monday—Thursday	4	94 (87—100)	
Friday			
Morning	1	91	
Afternoon	1	200	

^a TWA = time-weighted average.

ferent exposure models (exposure types I, II and III) were chosen which encompassed either constant or periodically varying m-xylene concentrations in the air and with or without intermittent physical exercise at 100 W. The features of the exposure types are illustrated in fig. 1, 2 and 3. Eight volunteer subjects participated in exposure types I and II and six subjects in type III.

The xylene concentration in the chamber air was adjusted to approximate the Finnish threshold limit value, either constant or time-weighted average (TWA), for xylene (4.1 mmol/m³, 100 ppm v/v), with a temporary elevation to a twofold higher level on the afternoon of the fifth day (Friday). The actual measured concentrations of m-xylene in the chamber air during the different types of exposure are presented in table 2.

Collection of samples

Venous blood samples were obtained through a teflon catheter inserted into a large forearm vein at specified time intervals, as in fig. 4 and 5 (in exposures I and II samples were taken immediately after the ergometer exercise sessions and at rest just before the next exercise).

Exhaled air was monitored over longer time periods on selected days for a few subjects of each exposure type with an apparatus which has been described in detail previously (20). Samples of forced *end-expiratory air* were collected in 250-ml polyester-lined polyethylene bags at specified times immediately after the venous blood sampling and at intervals throughout the postexposure period (fig. 4 and 5).

Urine samples were generally obtained at about 2-h intervals during exposure, and the subjects were asked to collect all urine voided throughout Monday night up until the beginning of the exposure period on Tuesday and from Thursday afternoon through the weekend (fig. 6, 7 and 8).

Analysis of samples

The gas chromatographic assays of *m-xylene* in *venous blood* and *end-expired air* have been described elsewhere (19). *Urinary m-methylhippuric acid* (more accurately, total conjugates of m-methylbenzoic acid) and *2,4-xyleneol* conjugates were also analyzed with gas chromatography (19, 20).

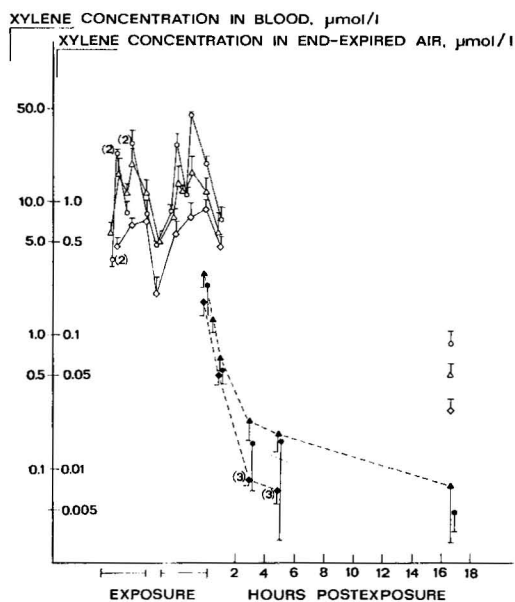


Fig. 4. Concentration of m-xylene in blood (open symbols) and end-expired air (closed symbols) during and after the first exposure day of exposure types I (triangles), II (circles), and III (diamonds). Mean values of 4–8 subjects are presented; bars denote standard deviations. For two subjects (number in parentheses) the means and ranges are given. For end-expired air, broken lines unite the point estimates of exposure types I and III.

Estimation of m-xylene uptake

For each type of exposure a theoretical estimate was made of the total uptake of m-xylene in the lungs (uptake = percentage of retention $\times$ inhaled xylene concentration $\times$ pulmonary ventilation $\times$ time) over a typical exposure day. Because it was not feasible in this study to monitor the pulmonary ventilation and pulmonary xylene retention of all the subjects or throughout the full length of the day, we measured these variables for two individuals as representatives of the whole group of volunteers during the exposures. The mean ventilation of these two subjects was 9.0 l/min at rest and 22.5 l/min over a 20-min period covering the 10-min ergometer exercise (5 min of exercise, 5 min at rest followed by another 5 min of exercise). For interindividual comparison among the volunteers, the pulmonary ventilation values at basal conditions, taken from standard tables (9), and during bicycle ergometer exercise of 100 W, performed in the laboratory, are given in table 1 for all the subjects.

The retention (R) of m-xylene in the lungs was calculated from the m-xylene

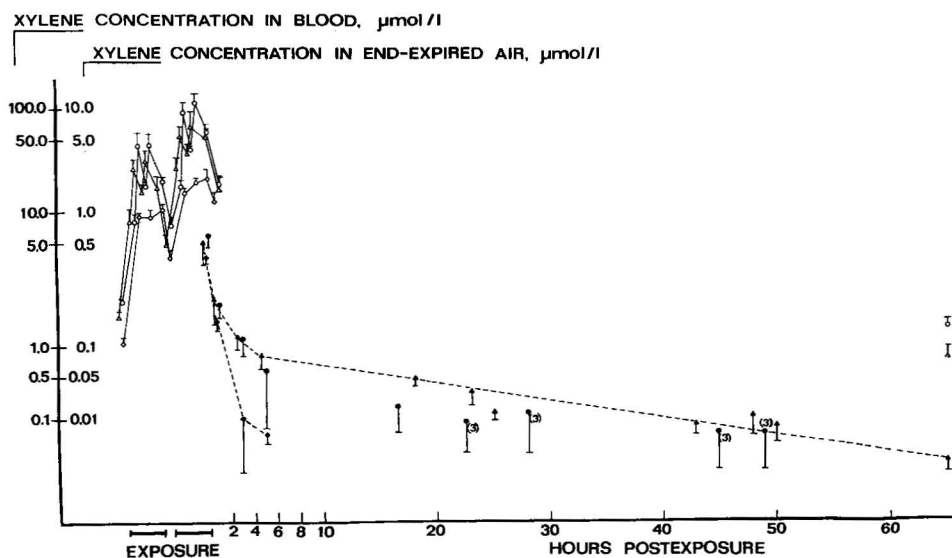


Fig. 5. Concentration of m-xylene in blood (open symbols) and end-expired air (closed symbols) during and after the fifth exposure day of exposure types I (triangles), II (circles), and III (diamonds). Mean values of 4–8 subjects are presented (number of fewer subjects given in parentheses); bars denote standard deviations. In exposure types I and II the blood samples were actually taken at the same points in time although they appear separated in the figure, and the higher concentration always followed the exercise. For end-expired air, broken lines unite the point estimates of exposure types I and III.

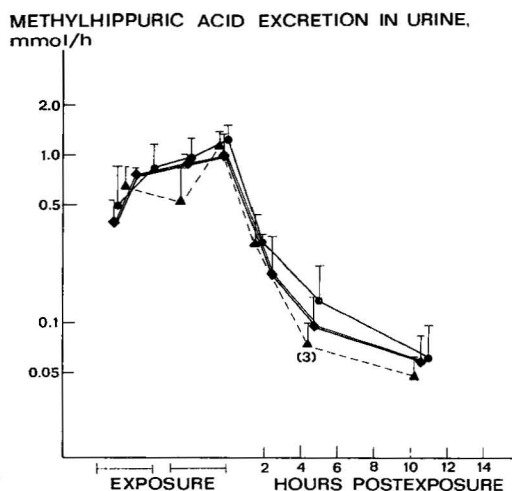


Fig. 6. Rate of methylhippuric acid excretion in urine during and after the first day of exposure type I (◆), II (●), and III (▲). Mean values of 4–8 subjects are presented (number of fewer subjects given in parentheses); bars denote standard deviations.

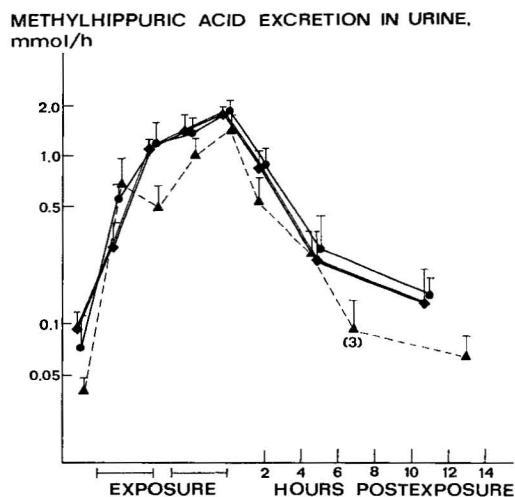


Fig. 7. Rate of methylhippuric acid excretion in urine during and after the fifth day of exposure types I (◆), II (●), and III (▲). Mean values of 4–8 subjects are presented (number of fewer subjects given in parentheses); bars denote standard deviations.

concentration in exhaled air (C_E) and chamber air (C_I) as $R = (C_I - C_E)/C_I$ for a few subjects participating in each exposure type and in different states of activity several times during a day's exposure.

Estimation of *m*-xylene excretion via the lungs

The postexposure exhalation of *m*-xylene after the first day of each type of exposure was calculated from the elimination curves of xylene based on the end-expired air samples (fig. 4). The elimination half-times were obtained graphically from the curves over the following three consecutive time periods: 0–3 h, 4–6 h and ≥ 17 h post-exposure [in the last case the half-time was obtained from the elimination curves after the fifth day (fig. 5)]. The corresponding elimination rate constants (k) were then calculated. It was observed that, by and large, the elimination curves of all three exposure types followed the same course, and the following rate constants were uni-

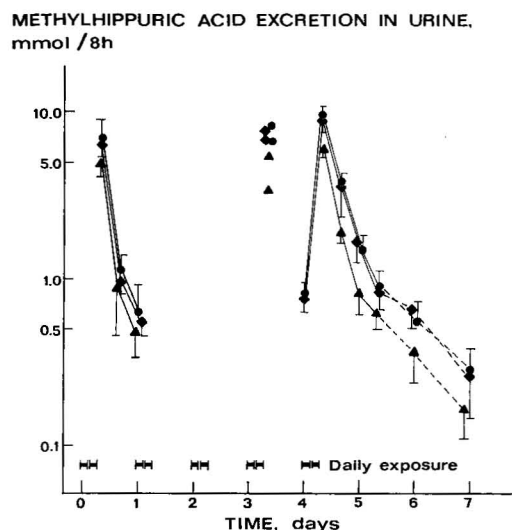


Fig. 8. Methylhippuric acid excretion in urine in 8-h periods in connection with five successive exposures to *m*-xylene of types I (◆), II (●), and III (▲). The mean values of 4–7 subjects are presented; bars denote standard deviations. For two subjects individual values are shown.