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THE TOXIC EFFECTS OF COMBINED EXPOSURE TO TOLUENE AND M-XYLENE IN ANIMALS. II. BLOOD TOLUENE AND M-XYLENE DURING SINGLE AND COMBINED EXPOSURE IN RATS

ZOFIA KORSAK, JERZY A. SOKAL and RADOSŁAW ŚWIERCZ

Department of Toxicology Evaluation, Institute of Occupational Medicine, Lodz, Poland

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Abstract. The influence of combined exposure to m-xylene and toluene vapours at a concentration of 100 + 100 ppm on blood m-xylene concentration in rats was investigated. Within 6–7 hours of coexposure to m-xylene and toluene a significant increase in blood m-xylene concentration, in comparison to single exposure to m-xylene at concentration of 100 ppm, was observed.

Study results may suggest that, reported earlier, the more than additive toxic effects of combined exposure to m-xylene and toluene in animals may result from its metabolic interaction.

INTRODUCTION

Combined exposure to various mixtures of organic solvents frequently occurs under industrial conditions, although actual exposure limits are set separately for single solvents. To overcome this inconsistency a well-known additivity formula is often used for the evaluation of the total combined exposure. It is assumed that the toxic effects of combined exposure to two or more solvents are additive in nature due to the similarities in their toxic effect and action mechanism. Our previous observations indicate the more than additive toxic effects of combined exposure to toluene and xylene (1 : 1) on the central nervous system and respiratory tract under acute and subchronic inhalation exposure (4, 7), the reasons for which are unknown. The more than additive toxic effects of toluene and xylene mixture could be the result of the mutual solvents metabolic inhibition reported by Ikeda (2). During combined

Address reprint requests to Z. Korsak, Department of Toxicology Evaluation, Institute of Occupational Medicine, P.O. Box 199, 90-950 Lodz, Poland.

exposure, the increased solvents concentration in blood may be suspected to be result of the metabolic interaction.

The aim of this study was to evaluate the toluene and m-xylene blood levels in rats during 7 hours inhalation exposure to toluene and m-xylene at concentration of 100 + 100 ppm.

MATERIALS AND METHODS

Male Wistar rats IMP DAK of body weight 450–500 g were exposed to vapours of m-xylene and toluene singly at a concentration of 100 ppm and in a mixture at a concentration of 100 + 100 ppm in a dynamic inhalation chamber (8 dm^3 volume) for 1 to 7 hours. Vapours of m-xylene and toluene were generated by heating liquid solvents in washers. The desired concentrations of vapours were obtained by diluting them with the air.

Concentrations of solvent vapours in the exposure chamber were measured every 30 min with the use of gas chromatography (Varian 1400 with FiD detector). The separation of solvents was performed using a 1.5 m metal column with 10% OV – 17 on chromosorb WHP (80/100 mesh) as a stationary phase at a column temperature of 100°C.

Seven groups of animals (each consisted of 4 rats) were exposed from 1 to 7 hours to m-xylene or toluene alone and another 7 groups of 4 rats were coexposed to the mixture of toluene and m-xylene. Immediately after cessation of inhalation exposure blood samples obtained from the tail vein were collected in heparinized glass capillaries of volume 200 μl. The contents of toluene and m-xylene in the rat blood were estimated by the head-space technique (5, 6) by using m-propylobenzene as an internal standard. Gas chromatograph (Varian 1400) with a FiD detector was used. Exposure concentrations of toluene and m-xylene were expressed in ppm;
1 ppm of toluene = 3.75 mg/m^3
1 ppm of m-xylene = 4.35 mg/m^3.

Toluene and m-xylene were supplied by the Polish Chemical Company and Reachim.

For statistical evaluation, analysis of variance (ANOVA) was used.

RESULTS

Data concerning the blood m-xylene levels during 7 hours' inhalation exposure to m-xylene at a concentration of 100 ppm and mixture of toluene and m-xylene at a concentration of 100 + 100 ppm are presented in Fig. 1.

During the single exposure the concentration of m-xylene in the blood increased rapidly within the first 2 hours, then settled down and reached a level of 9 μmole/dm^3 at the end of 7 hours of exposure.

Coexposure to m-xylene and toluene resulted in the rapid increase of blood m-xylene concentration in the first 2 hours of exposure, then settled, and

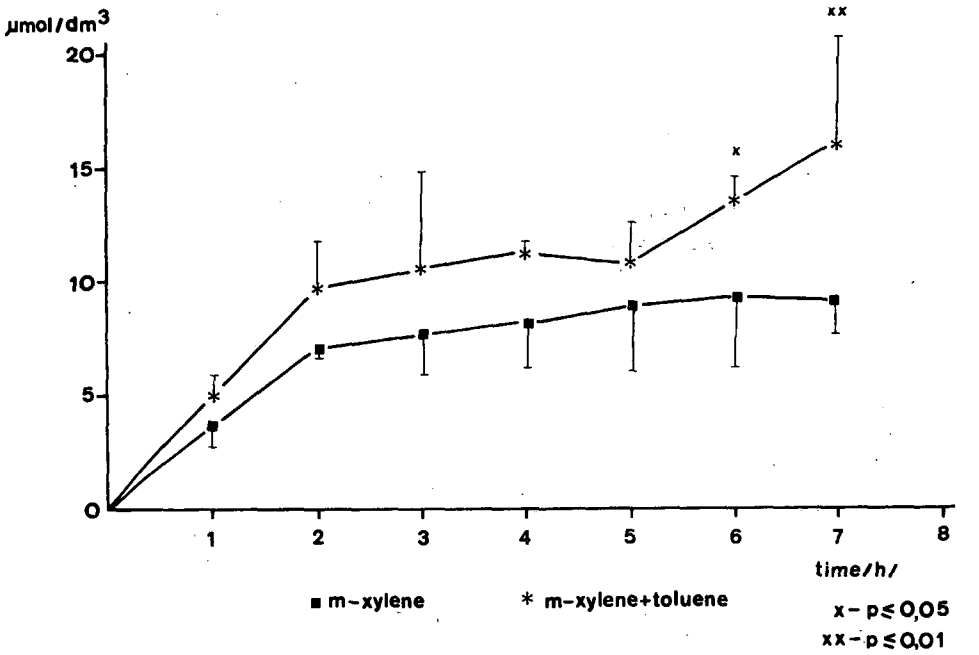

Fig. 1. m-Xylene in blood of rats during 7 hours inhalation exposure to m-xylene at a concentration of 100 ppm and a mixture of m-xylene and toluene at concentraion of 100 + 100 ppm. Each point represents the mean value of separate measurements in 4 rats ± SD.
A statistically significant difference in comparison to single m-xylene exposure is denoted as x (for $p \leqslant 0.05$) and for xx ($p \leqslant 0.01$).

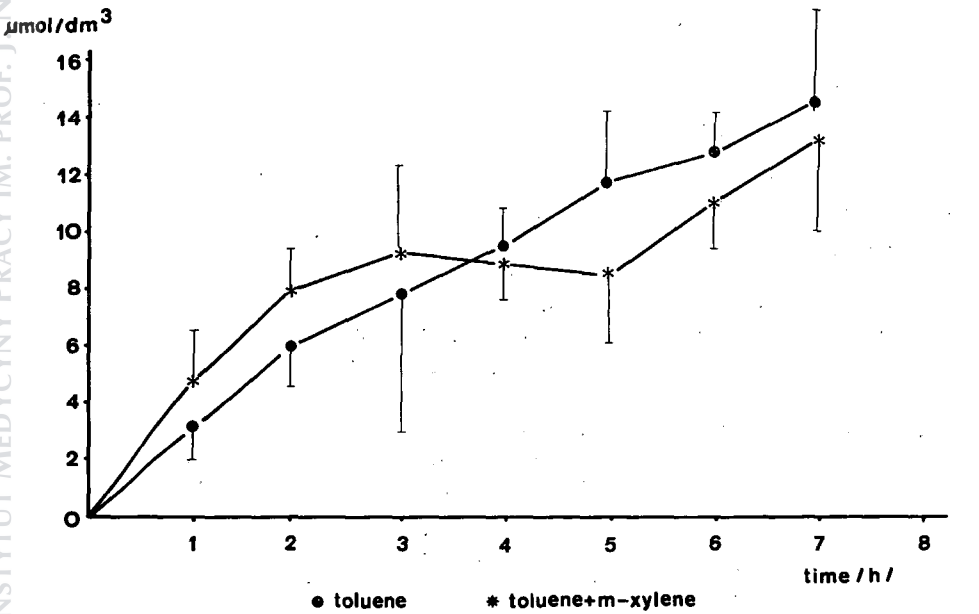

Fig. 2. Toluene in blood of rats during 7 hours inhalation exposure to toluene at a concentration of 100 ppm and a mixture of toluene and m-xylene at a concentration of 100 + 100 ppm. Each point represents the mean value of separate measurements in 4 rats ± SD.

a rapid increase was observed again in the 6–7th h of exposure. In the seventh hour, blood m-xylene reached a level of 16 μmol/dm^3. In the 6th and 7th hour of coexposure to m-xylene and toluene, the concentration of m-xylene in the blood was statistically higher in comparison to that observed during a single exposure to m-xylene.

No statistically significant differences in blood toluene concentrations were observed during single 7 hours exposure to toluene at a concentration of 100 ppm as well as during coexposure to toluene and m-xylene at a concentration of 100 + 100 ppm (Fig. 2).

DISCUSSION

Our results indicate that an observed statistically significant higher concentration of blood m-xylene in rats after 6 to 7 hours of exposure to a mixture of m-xylene and toluene may cause engender more than additive toxic effects of combined exposure to toluene and xylene (4, 7). The higher level of m-xylene in the blood of animals coexposed to m-xylene and toluene might be the result of higher m-xylene absorption or inhibition of its biotransformation. It has been shown in volunteers that retention of xylene is not affected by the presence of other solvents in inhaled air (8). A similar effect also may be assumed in rats.

At a higher level of exposure, inhibitory metabolic interaction between toluene and xylene has been reported (2). Also a decrease has been reported (8) in methylhippuric acid in volunteers exposed to a mixture of xylene and other solvents (100–150 mg/m^3).

Other authors' reports have showed that in volunteers exposed to mixture of m-xylene (300 mg/m^3) and toluene (170 or 260 mg/m^3) the urinary excretion of methylbenzoic acid was lower in comparison to that observed during a single exposure to m-xylene (300 mg/m^3). Statistics, however, taken during a 4 hour exposure or within a 22 hour exposure, were not significantly different (3). The study results also showed a higher blood m-xylene concentrations in rats coexposed to m-xylene and toluene in comparison to single m-xylene exposure within a 4 hour exposure. Statistically significant differences observed only within 6–7 hours of exposure.

It has been reported that during exposure to m-xylene vapours, rats' biotransformation capacity is sufficient to metabolise the dose observed at the concentration of 800 mg/m^3 (1). This value was established, however, for a single m-xylene exposure and probably cannot be applied simply in the case of combined exposure to m-xylene and toluene. The parallel examination of urine m-xylene metabolite is necessary to dissolve the still existing doubts as to whether the significantly higher blood m-xylene concentration (6–7 hours of exposure) observed in rats coexposed to m-xylene and toluene at a concentration of 100 + 100 ppm is a result of their toxicokinetic interaction.

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