International Journal of Occupational Medicine and Environmental Health, Vol. 8, No 4, 361 – 365, 1995

KINETICS OF N-BUTYL ALCOHOL AND M-XYLENE IN BLOOD DURING SINGLE AND COMBINED INHALATION EXPOSURE IN RATS

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Key words: n-Butyl alcohol, m-Xylene, Blood levels, Combined exposure, Headspace analysis

Abstract. The levels of m-xylene and n-butyl alcohol in blood of rats during single and combined inhalation exposure to m-xylene and n-butyl alcohol at the concentrations of 100 + 100 ppm were investigated. We found that levels of n-butyl alcohol and m-xylene in blood of animals during single exposure did not differ as compared to coexposure. It has been shown that less than additive neurotoxic and irritating respiratory tract effects of m-xylene and n-butyl alcohol mixture, observed earlier under acute and subchronic inhalation study, cannot be explained by their metabolic interaction.

INTRODUCTION

In industrial as well as in communal conditions the risk of exposure to organic solvents is high. Although exposure to the mixture of solvents is of more frequent occurrence than that to one solvent the exposure limits are set separately for single solvents. The assumption of additivity of toxic effects is used in industrial hygiene to cope with the problem of combined exposure to solvents. In the previous study more than additive effect of toluene and xylene (1:1) mixture was shown (4,6,16). Toluene and m-xylene concentrations determined in blood of rats exposed to vapours of m-xylene or toluene at the concentration of 100 ppm and to their 1:1 mixture at the concentration of 100 + 100 ppm, confirmed more than additive toxic effects of combined exposure to toluene and m-xylene. Our interest in toxic effect of combined exposure to m-xylene and n-butyl alcohol results from frequent simultaneous occurrence of these solvents in the work environment. In Poland the number of people exposed to xylene reaches about 12 000, among them, about 4 000 are exposed to concentrations which exceed threshold limit value-time weighted average (TLV-TWA) (1). Wesołowski (1994, personal communication) determined average xylene concentration in air of 21.6 mg/m^3 and n-butyl alcohol of 1.5 mg/m^3 in the paint and varnish factories. In Finnish furniture factories average concentration of xylene in

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the work environment was 19 ppm (82.7 mg/m^3) and butanol 17 ppm of (51.5 mg/m^3) (12). It is estimated that in Poland exposure to n-butyl alcohol in the work environment concerns about several thousand people (2). Butanol occurs in many alcoholic drinks, including beer, which increases the group of exposed people (3).

The aim of this study was to investigate the kinetics of n-butyl alcohol and m-xylene in blood during single and combined inhalation exposure in rats. For this purpose their blood concentrations were determine during 7 hours of single inhalation exposure to m-xylene and n-butyl alcohol at the concentration of 100 ppm, and during combined exposure to these solvents at the concentrations of 100 + 100 ppm.

MATERIALS AND METHODS

Chemicals

n-Butyl alcohol and m-xylene were supplied by the Polish Chemical Reagent Company and the Reachim. Conversion factors (25 C; 760 mm Hg): n-butyl alcohol 1 ppm = 3.03 mg/m^3, m-xylene 1 ppm = 4.35 mg/m^3.

Animals and inhalation exposure

Male Wistar rats Imp: DAK of body weight 450–500 g were exposed to vapours of n-butyl alcohol or m-xylene at the concentration of 100 ppm and to their 1:1 mixture at the concentrations of 100 + 100 ppm in a dynamic inhalation chamber (8 dm^3 volume). Vapours of n-butyl alcohol and m-xylene 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 by means of gas chromatography (Varian 1400) with a flame ionization detector (FID) using 3 m metal column with 10% OV-17 on chromosorb WHP (80/100 mesh) as a stationary phase at a column temperature of 70°C (5,6). Seven grups of animals, 4 rats each, were exposed for 1 to 7 hours to n-butyl alcohol or m-xylene and another 7 groups of 4 rats were exposed to the mixture (1:1) of n-butyl alcohol and m-xylene.

Blood samples

Immediately after cessation of inhalation exposure, blood samples obtained from the tail vein were collected in heparinized glass capillaries of 200 ul volume. The contents of n-butyl alcohol and m-xylene in the rat blood were estimated by gas chromatography with the headspace technique (9,13) by using n-pentanol and n-propylobenzene as an internal standard. Gas chromatograph (Hewlett Packard 5890) equipped with FID was used. The glass column was (2 m × 2 mm id.) packed with 20% SE-30 on Chromosorb WHP (100–120 mesh). The column working temperature was 70°C.

Statistics

For statistical evaluation analysis of variance (ANOVA) and the Scheffe's test (15) were used.

RESULTS

Mean concentrations of solvent vapours in inhalation chamber were: for n-butyl alcohol – 94 ± 9 ppm (285 mg/m^3); for m-xylene – 90 ± 5 ppm (392 mg/m^3), and for mixture of n-butyl alcohol and m-xylene 97 ± 8 ppm + 96 ± 8 ppm (294 + + 418 mg/m^3), respectively.

Data concerning the blood n-butyl alcohol concentrations during 7 hours of inhalation exposure to n-butyl alcohol and to mixture of n-butyl alcohol and m-xylene at the concentration of 100 + 100 ppm are presented in Fig. 1.

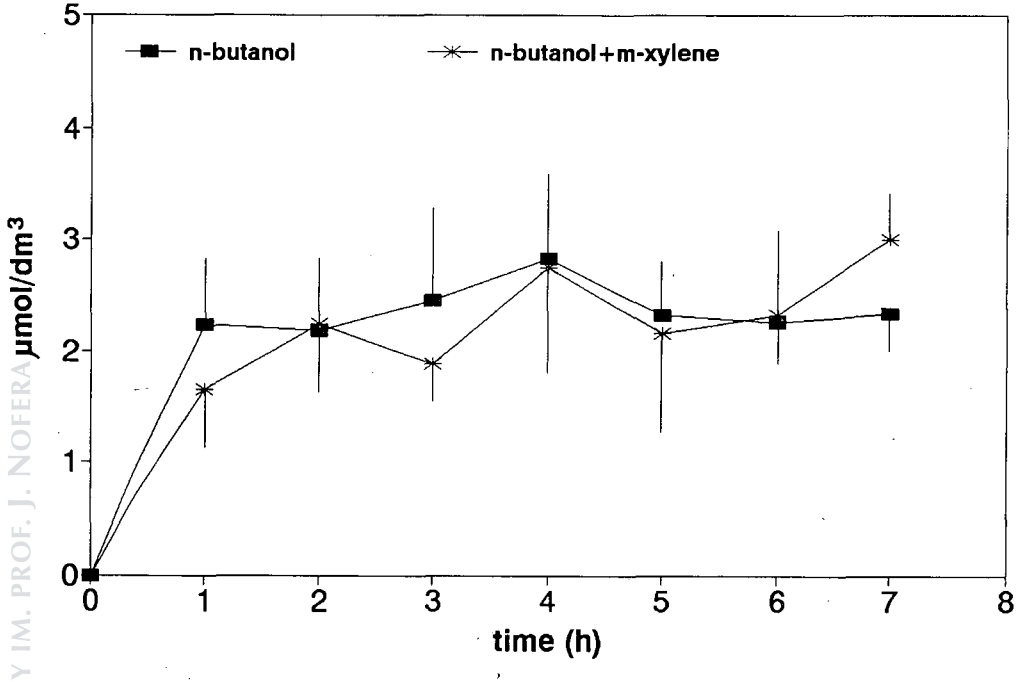

Fig. 1. n-Butanol in blood of rats during a 7-hour inhalation exposure to n-butanol at the concentration of 100 ppm and a mixture of n-butanol and m-xylene at the concentration of 100 + 100 ppm. Each point represents the mean value of separate measurements in 4 rats ± SD.

During a single exposure the concentration of n-butyl alcohol in blood increased rapidly within the first hour, then settled to a level of 2.2 µmol/dm^3. In the fourth hour, concentration of n-butyl alcohol in blood reached a maximum level of 2.8 µmol/dm^3.

Coexposure to n-butyl alcohol and m-xylene resulted in a rapid increase of blood n-butyl alcohol concentration in the first 2 hours of exposure, then settled to a level of 2.2 µmol/dm^3. In the seventh hour, the level of n-butyl alcohol in blood reached maximum of 3.0 µmol/dm^3.

Data concerning the blood m-xylene levels during 7 hours of inhalation exposure to m-xylene at the concentration of 100 ppm and to mixture of m-xylene and n-butyl alcohol at the concentration of 100 + 100 ppm are presented in Fig. 2.

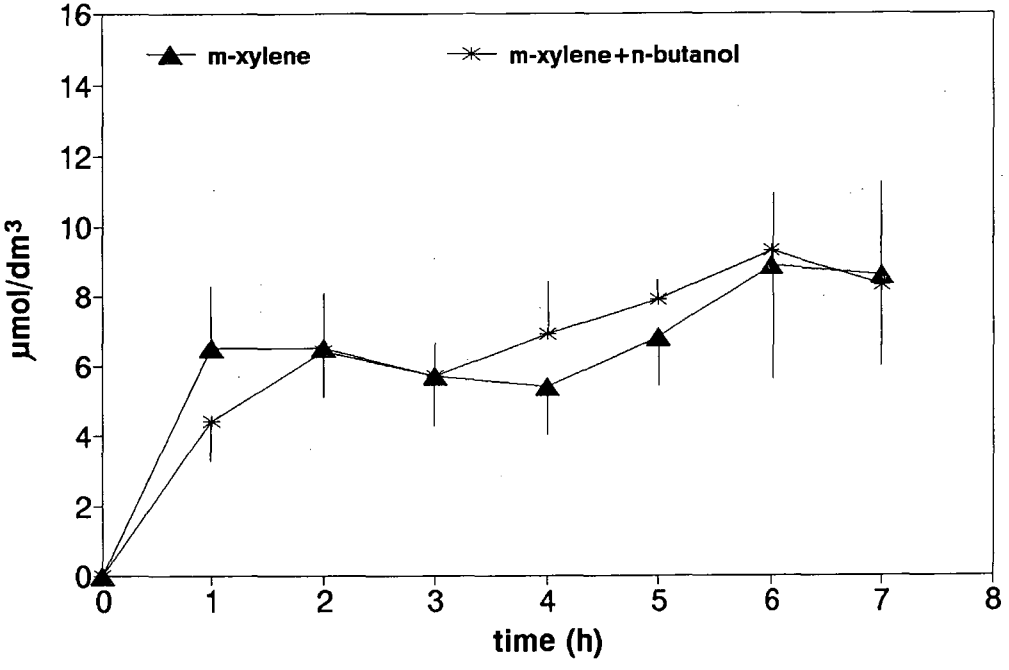

Fig. 2. m-Xylene in blood of rats during a 7-hour inhalation exposure to m-xylene at the concentration of 100 ppm and a mixture of m-xylene and n-butanol at the concentration of 100 + 100 ppm. Each point represents the mean value of separate measurements in 4 rats ± SD.

During a single exposure the concentration of m-xylene in blood increased rapidly within the first hour, then settled at the level of 6.5 µmol/dm^3 and at the end of the seventh hour of exposure reached the level of 8.6 µmol/dm^3.

Coexposure to n-butyl alcohol and m-xylene resulted in a rapid increase of blood m-xylene concentration in the first 2 hours of exposure, then settled to a level of 6.4 µmol/dm^3. In the seventh hour, blood m-xylene reached the level of 8.3 µmol/dm^3. No statistically significant differences in blood n-butyl alcohol and blood m-xylene concentrations were observed during the single exposure and coexposure.

DISCUSSION

No statistically significant differences in the concentration of solvents in the rat blood between single or combined exposure were found. The level of n-butyl alcohol and m-xylene in blood of animals during a single exposure did not differ as compared to coexposure. The results showed that their metabolic interaction is neglegible.

These results are comparable with those published earlier in humans (Jakubowski and Kostrzewski, 1989), in which volunteers were exposed to m-xylene at concentrations of about 45 and 70 ppm and to m-xylene and n-butyl alcohol at concentrations of about 90 and 140 ppm. The authors did not observe statistically significant difference in excretion of methylbenzoic acid in urine during a 4-hour exposure or within 22 hours after termination of exposure.

The observed in our earlier studies less than additive toxic effect during acute and subchronic exposure to mixture of m-xylene and n-butyl alcohol cannot be justified by metabolic interaction of these solvents (7,8,16). m-Xylene is metabolized mainly by cytochrome P-450 (145) and n-butyl alcohol by alcohol dehydrogenase (17). It seems that at the concentrations used in this study m-xylene and n-butyl alcohol do not compete for metabolizing the enzyme system.

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Received for publication: July 3, 1995
Approved for publication: September 27, 1995