Industrial Health, 1992, 30, 139—144

LETTER TO THE EDITOR

Evaluation of Mixed Exposure to Organic Solvents by Estimating Their Metabolites in Urine

Key words: Evaluation-Coexposure-Organic solvent-Urinary metabolite

Many organic solvents are used in mixtures. For example, thinner for paint may be composed of toluene, xylene, ethylbenzene, methylethylketone and acetone or of two or more of these substances with some other compounds. Thus, many workers are exposed to a mixture of solvents. However, untill 1970[1] when a study on coexposure to toluene and xylene was reported, there had been no method for evaluation of mixed exposure by analyzing the urinary metabolities. Now in Japan[2], industrial haelth administration consists of working environment control'"), work practice management and health care. The haelth care program includes periodical biological monitoring of workers exposed to lead and eight kinds of organic solvents, including mixed ones since October 1, 1989, when the amendments to the Ordinance on Prevention of Lead Poisoning and the Ordinance on Prevention of Organic Solvents Poisoning were issued by the Ministry of Labor[5,6]. The biological monitoring and the periodical health surveillance were carried out at every 6 months. The solvents implemented for biological monitoring of their metabolites in urine are toluene, xylene, styrene, trichloroethylene, tetrachloroethyrene, 1, 1, 1,–trichloroethane, N, N-dimethylformamide and n-hexane. State of health risk in relation to actual working situation including working environment, work methods and working conditions may be suggested from the results of biological measurements').

Mori et al.[3] made a survey on the kind of organic solvents used in 237 workshops in the Kyushu district and reported that the number of workshops using mixed solvents reached 79.2% of the surveyed workshops. Thus there is need for the estimation and evaluation of health risk of workers exposed to mixed solvents by monitoring urinary metabolites.

As to the metabolic rates of mixed solvents from the view of pharmacokinetics, two cases should be taken into consideration. One is the case in which little mutual effects on the metabolic rates of components are observed in workers exposed to mixed organic solvents[1,9,10] and the other is that marked mutual effects are observed on the metabolic rates in workers exposed to mixed solvents containing two or more kinds of solvents[11,12].

A study made by Ogata et al[1] was a former case in which volunteers were coexposed to the vapor of 67 ppm toluene and 83 ppm xylene in a mixed state for three hours in an artificial exposure chamber and their urinary hippuric acid and methylhippuric acid were determined. The report suggested that simultaneous exposure did not alter the rates of excretion of both metabolites from those for separate exposure.

Recently, Tardif et al[9] described that simultaneous exposure to 50ppm toluene and 40ppm xylene for 4 hours in a controlled exposure chamber did not show the mutual effects on the concentrations of the solvents themselves in blood and exhaled air as well as on the urinary concentrations of hippuric acid and methylhippuric acid. The same authers also showed that simultaneous exposure to 95ppm toluene and 80ppm xylene caused significant delay in the urinary excretion of hippuric acid but not of metylhippuric acid.

Kawai et al.[10] monitored urinary metabolites of workers exposed to a mixture of 11.0ppm toluene, 7.1ppm styrene and 32.6ppm methanol and reported that no modification in metabolism was induced by the combined exposure at these low exposure levels.

These three reports suggest that the mutual metabolic interactions among the multiple components of solvents will not likely occur in humans who are exposed to such mixtures as toluene and xylene, or toluene, xylene and methanol in the lower concentration ranges than those reported in the above studies.

For the evaluation of mixed exposure to organic solvents from their metabolites, the ACGIH concept of evaluation of workplace air for mixed organic vapors with their airborne concentrations and of the threshold limit values (TLVs) can be applied, replacing the TLVs with the biological exposure indices (BEIs) and the airborne concentrations in breathing zone (C) with metabolite concentrations (MC) under the assumptions described below. According to the ACGIH proposal[13], the workplace air with multiple organic vapor is evaluated with the sum of fractions as follows,

$$C_1/T_1 + C_2/T_2 + \cdots\cdots C_i/T_i + \cdots\cdots C_n/T_n = K \qquad (1)$$

in which C_i denotes the airborn concentration of the ith component and T_i does the TLV for the same component. If the K value exceeds unity, the workplace is evaluated to exceed the exposure threshold for the mixed vapors. If the effect of the mixed components is synergistic or independent considered from the pharmacodynamic point of view, the equation (1) is not applicable. Applying equation (1), the biological exposure indices for mixed organic solvents are evaluated only when the metabolic rates have no cross effects as described in the following section 1).

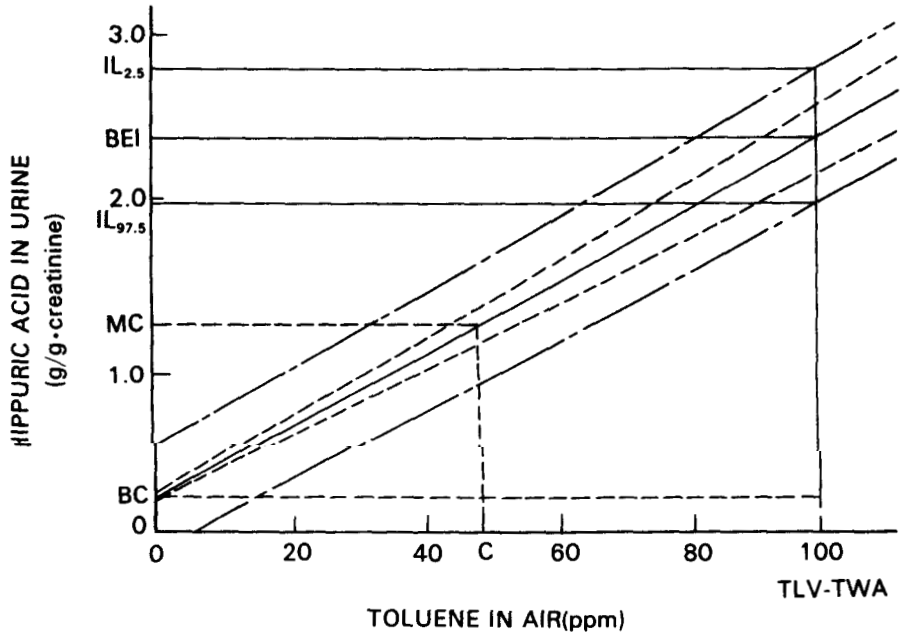

Fig. 1. Correlation of toluene concentration in air with hippuric acid in urine[15]. Regression equation is expressed as straight line in center, 95 per cent confidence ranges of regression line are as dotted lines close to the regression line and 95 per cent predictive ranges of individual samples are as *chain* linea at the outermost. Symbols of $IL_{2.5}$, and $IL_{97.5}$ are 2.5 per cent and 97.5 per cent predictive concentration of hippuric acids in individual samples, respectively which corresponded with TLV of 100 ppm toluene.

1) Compounds that have no cross effect on urinary metabolites:

In order to apply the concept of additive effects of multiple organic vapors to biological exposure indices, by the following equation (2), the following assumptions are presumed; The threshold limit values **(TLVs)[13]** and biological exposure indices (BEIs)[14] apply to eight-hour exposure, five days a week. The BEIs apply to moderate work load and absence of non-occupational exposure. The BEIs also represent the level of metabolites which are most likely observed in urine collected from a worker who has been exposed to TLV of solvent **vapor[14]**.

Figure 1 shows the regression lines between toluene concentration in breathing zone air and hippuric acid concentration in urine of a group of workers[15]. **In** this figure, average hippuric acid concentration in urine corresponding to TLV of 100ppm toluene (IL,) is **2.4** g/g-creatinine. The concentration of **2.4** g/g-creatinine is close to the BEI of ***2.5*** g/g-creatinine. The results of Fig 1 indicate that C/TLV for toluene is the same with (MC-BC)/(BEI-BC) for hippuric acid, where BC indicates backgroud concentration.

As shown in this figure, it should be noted that individual differences in urinary metabolites are found in a worker group exposed to the same exposure

concentration of toluene which are expressed by **95** percent predictive range of individual values between the two lines of $IL_{2.5}$ and $IL_{97.5}$. These interindividual differences are recognized in the metabolite concentrations of workers exposed to single **solvents**[1,9,10]. **Thus** (MC–BC) for C and (BEI–BC) for TLV can be accepted with confidence ranges with margin of error. However, individual differences in the concentration of hippuric acid in the volunteers, expressed **as** standard deviation or **as** the coefficient of variation, for an airborne cmcentration of toluene in the breathing zone and those of methylhippuric acid for a concentration of xylene are different in their values from those given in both **reports**[1,9]. Thus we used average values of the concentrations of urinary metabolites corresponding to airborne concentrations of solvents in the breathing zone in the present report.

Thus TLV is replaced with BEI in the above equation **(1)** according to the following method: In the range within which C is proportional to (MC–BC) and TLV–TWA is corresponding to (BEI–BC), equations of $C=k'$ (MC–BC) and $TLV=k'$ (BEI–BC) can be induced. Thus,

$$C_i/TLV_i=(MC_i-BC_i)/(BEI_i-BC_i), \text{ then}$$

$$(MC_1-BC_1)/(BEI_1-BC_1)+(MC_2-BC_2)/(BEI_2-BC_2)+\cdots\cdots$$
$$(MC_i-BC_i)/(BEI_i-BC_i)+\cdots\cdots(MC_n-BC_n)/(BEI_n-BC_n)=k \qquad (2)$$

The symbol BC can be eliminated if the background level of the indicator is zero or negligible compared to the level produced by exposure.

2) Compounds that have cross effects on urinary metabolites:

In the case of competitive inhibition, metabolism is reduced during coexposure, consequently the concentrations of urinary metabolites are reduced. For example, ethanol intake prior to several hours or just before inhalation exposure to organic solvents reduces the urinary metsbolite **excretion**[16] and the counterplan for this phenomenon is described in the Japanese Government Ordinance[6].

These cases are expressed by the equation,

$$(MC-BC)/(BEI-BC)<C/TLV.$$

On the contrary, when microsomal enzyme activity is induced by chronic alcohol intake, urinary metabolites of organic solvents **increased**[16]. In this case, a relation of $(MC-BC)/(BEI-BC)>C/TLV$ is found.

However, the degree of inhibition or of induction of metabolisms depends on the kinds and/or the cocentration of the coexistent solvents.

The application of the equation to the cases of mixed solvent exposures:

The adoption of the equation (2) is useful for mixed exposure to toluene and m-xylene') reported previously by the author.

The urinary concentration of volunteers at the end of the shift was 1.4 g/g-creatinine for hippuric acid and 1.7 g/g-creatinine for methylhippuric acid. The BEI of hippuric acid for 100 ppm (TLV-TWA) of toluene is 2.5 g/g-creatinine and of methylhippuric acid for 100 ppm (TLW-TWA) of m-xylene is 1.5 g/g-creatinine. The background level (BC) of hippuric acid was 0.2 g/g-creatninine. The value obtained by equation (2) is $(1.4-0.2)/(2.5-0.2)+1.7/1.5=1.65$. Thus the sum of the fraction of combined metabolites (1.65) derived by equation (2) corresponds to the sum of the fractions of the airborne concentration (1.5) obtained by equation (1).

In the present report, the authors have proposed a fundamental method for the evaluation of biological monitoring for mixed exposure. It should be noted that its application is limited to such cases of the kinds of solvents and to the concentration range of solvents for which the data[1,9,10] have been reported. A more general application of the equation will be attained after more experimental and field data have been accqmulated.

REFERENCES

1) Ogata M, Tomokuni K, Takatsuka Y. Urinary excretion uf hippuric acid and m- or p-methylhippuric acid in the urine of persons exposed to vapours of toluene and m- or p-xylene as a test of exposure. Brit. J. Ind. Med. 1970; 27: 43–50.

2) Ogata M. Goals and activities of the biological monitoring group in Japan. In; Fiserova-Bergerova V, Ogata M, eds. Biological monitoring of exposure to industrial chemicals. ACGIH, Cincinnati, OH, 1990; 3–6.

3) Sakabe H. Proceedings of Govermental Seminor held at ACGIH Conference. May 31, 1979. In transaction of the 41 annual meeting ACGIH, Cincinnati, OH, 1979; pp.71–83.

4) Sakabe H, Ikeda M, Kosi S, Tada O, Toyama T, Hara I, (supervised by Working Environmental Improvement Office, Ministry of Labour). Working environment measurement system in Japan. Japan Association for Working Environment Measurement, Tokyo, 1991 1–10.

5) Labour Standard Bureau, Ministry of Labour. Ministry of Labour Notification No 462. Implementation of partial amendment of Industrial Safety and Health Law, Partial amendment of Prevention of Organic Solvent Poisoning and partial amendment of Prevention of Lead Poisoning (August 22 1989).

6) Labour Standard Bureau, Ministry of Labour. Ministry of Labour Notification No 463. Notification of collection time and storage of blood and urine and qualification of omission of subjects in health examination in examination in Ordinance of Prevention of Organic Solvent Poisoning No 29 nad Prevention of Lead Poisoning No. 53 (August 23 1989).

7) Ogata M, Biological monitoring, In: Ogata M, Harada A, Inoue N, Kono K (supervised by Industrial Health Division, Labour Standard Bureau, Ministry of Labour). Metehod on Health Examination for Workers Exposed to Organic Solvents, 76–107.

8) Mori K, Fujishiro K, Ueda R, Simizu K, Inoue N. Present condition on how to select organic solvents on checkup. Jpn. J. Ind. Health 1992; 34: 144-5.

9) Tardif R, Lepare, S, Plaa G. L, Brodeur J. Effect of simultaneous exposure to toluene and xylene on their respective biological exposure indices in humans. Int. Arch. Occup. Environ. Health; 1991; 63: 279–84.

10) Kawai T, Yasugi T, Mizunuma K, Horiguchi S, Morioka I, Miyashita K, Uchida Y, Ikeda M. Monitoring of workers exposed to a mixture of toluene, styrene and methanol vapour by means

of diffuse air sampling, bood analysis and urinalysis. Int. Arch. Occup. Environ. Health; 1992; 63 : 429–35.

11 Inoue O., Seiji K. Watanabe T, Kasahara M, Nakatsuka H, Yin S-N. Li G-L, Cai S-X. Jin C, Ikeda M. Mutual metabolic suppression between benzene and toluene in man. Int. *Arch.* &up. Environ. Health 1988; 60 : 15–20.

12 Liira J, Rihimaki V, Engstrom K, Pfaffli P. Coexposure of man to ut-xylene and methyl ethyl ketone. *Scan.* J. Work Environ. Health 1988; 14: 322–7.

13 Chemical substances TLV committee (Chairman, Doull T.) Threshold limit values for mixtures, In; 1991–1992 Threshold limit values and biological exposure indices. ACGIH. Cincinnati, 1991; 48–50.

14 Biological Exposure Indices Committee (Chairman, Thomas V.) Biological Exposure Indices, In: 1991–1992 Threshold limit values and biological exposure indices. ACGIH. Cincinnati, 1991: 58 –70.

15 Ogata M, Estimation of solvent concentration in ambient air from urinary metabolite levels of workers exposed to solvents. Industrial Health 1984; 22: 319–24.

16 Sato A, Endoh K, Kaneko T, Yonekura I. Physiological and environmental factors affecting biological monitoring of exposure to organic solvent vapors. Jpn. J. Ind. Health 1993; 33: 3–16.

Department of Medical Social Work,
Kawasaki University of Medical Welfare.
Matushima 288, Kurashiki City, 701-01, Japan

Masana OGATA

Department of Anesthesiology
University of Miami School of Medicine
1550 NW 12th Avenue, Miami FL 33136. USA

Vera FISEROVA-BERCEROVA (THOMAS)

(Received April 30, 1992 and in revised form December 16. 1992)