# Exposure of workers to a mixture of toluene and xylenes. II Effects

Zhen Chen, Shi-Jie Liu, Shi-Xiong Cai, Yi-Min Yao, Hong Yin, Hirohiko Ukai, Yoko Uchida, Haruo Nakatsuka, Takao Watanabe, Masayuki Ikeda

**Institute of Occupational Medicine, Chinese Academy of Preventive Medicine, Beijing, China**
Z Chen
S-X Cai

**Beijing Medical University School of Public Health, Beijing, China**
S-J Liu
H Yin

**Institute for Prevention and Treatment of Occupational Diseases, Bureau of Chemical Industry, Beijing City, Beijing, China**
Y M Kao

**Department of Public Health, Kyoto University Faculty of Medicine, Kyoto 606-01, Japan**
H Ukai
Y Uchida
M Ikeda

**Kyoto Industrial Health Association, Kyoto 604, Japan**
H Ukai

**Department of Environmental Sciences, Tohoku University School of Medicine, Sendai 980, Japan**
H Nakatsuka

**Miyagi University of Education, Sendai 980, Japan**
T Watanabe

Requests for reprints to: Professor M Ikeda, Department of Public Health, Kyoto University Faculty of Medicine, Kyoto 606-01, Japan.

Accepted for publication 19 April 1993

## Abstract

**The health effects of exposure to a mixture of toluene and xylene isomers was studied on the fourth or fifth days of a working week in factories in China. The study population comprised 233 subjects (122 men and 111 women), who were exposed to the time weighted geometric mean (maximum) concentrations of toluene (3 (203) ppm) and xylenes (4 (103) ppm). For comparison, 241 non-exposed controls (116 men and 125 women) were recruited from the same regions. The prevalence of some subjective symptoms significantly increased in the exposed population, and the symptom profiles were similar to those found after exposure to toluene or xylenes alone. Haematology and serum biochemistry did not show notable changes. It seems reasonable to conclude that the effects of the toxicities of toluene and xylenes in combination are additive.**

(*Occup Environ Med* 1994;51:47–49)

Toluene (methylbenzene) and xylenes (three isomers of dimethylbenzene) are often present in combination in organic solvent preparations.[1-3] Many reports from various countries have been published on exposure of workers,[4-11] or of the general population.[12 13] Whereas the toxicity of toluene has been extensively studied, reports on the health effects of xylenes alone are few; publications of the effects of toluene-xylene combinations on factory workers are rare, despite their wide use.

More than 200 workers exposed to toluene and xylenes in combination were examined in our study and compared with a similar number of non-exposed controls in a search for possible effects on the central nervous system, as well as haematological and serum biochemical effects. The lack of metabolic interaction between the solvents is reported separately.[14]

## Materials and methods

### SELECTION OF WORKERS AND DESIGN OF HEALTH EXAMINATION

The study was carried out in China on the fourth or fifth day of a working week.[14] The criteria of selection were that (1) the workers participated in the whole examination (personal diffusive sampling,[15-17] analysis of urine for monitoring of exposure, a questionnaire, haematology, and serum biochemistry for examination of effects on health), and (2) exposure was almost exclusively to toluene and xylenes (>90%), but not toluene alone (no more than 90% toluene[18]), xylenes alone (not more than 70% xylenes[19]), or gasoline.

It was not possible beforehand to identify the workers who met the criteria. Accordingly, almost 1000 exposed workers were examined, of whom 233 subjects (122 men and 111 women) satisfied the two selection criteria. Some of them were exposed also to a few ppm ethylbenzene, but none was exposed to benzene.[14] Non-exposed controls of 116 men and 125 women were recruited from the clerical sections of the same factory or factories in the same regions. Table 1 shows that there was no significant age difference between the sexes or between exposed and non-exposed populations. ($p > 0.05$ for both). Most exposures were low[14] with less than 10 ppm (geometric mean) for the sum of all exposures, although some workers were exposed to toluene and xylenes in excess of the current occupational exposure limit of 100 ppm of each.[20-22]

Health examination both for the exposed and for the non-exposed persons consisted of (1) interview by a doctor or a public health nurse for medical history and completion of questionnaires, (2) blood sampling for haematology and serum biochemistry for liver and kidney functions, (3) collection of urine for clinical urinary analysis by diagnostic kits, and (4) clinical examination (for details, see Ukai *et al*[18]). Urine samples for metabolite analyses were collected at the end of the shift and on another separate occasion.[23] The questionnaire has 12 questions on the symptoms during work and 57 questions (two additional questions for women on menstruation) for the past three months (when not at work).[24 25] The prevalence of the subjective symptoms was calculated after Ukai *et al*[18] as: the number of affirmative answers by the group/(the number of the people in the group) × (number of questions) × 100 (%).

*Table 1 Mean (y) age of exposed and control workers*

| *Workers* | *Men (SD, n)* | *Women (SD, n)* | *Men and women (SD, n)* |
|---|---|---|---|
| Exposed | 30·9 (8·0, 122) | 31·9 (7·2, 111) | 31·4 (7·6, 233) |
| Controls | 33·8 (9·2, 116) | 31·8 (7·1, 125) | 32·8 (8·3, 241) |

### STATISTICAL ANALYSIS

Significant differences in prevalences were tested for with the $\chi^2$ test, in means with a $t$ test (one tailed) and in distribution with the Mann-Whitney U test.

*Table 2 Prevalence of subjective symptoms*

| Subjective symptoms | Sex | No of questions | Controls | Exposed to toluene and xylenes | | |
|---|---|---|---|---|---|---|
| | | | | Total | 1–20 ppm | >21 ppm |
| During work | Men | 12 | 71 (116):5·1 | 274 (122): 18·7** | 226 (91):20·7 | 48 (31):12·9 |
| | Women | 12 | 44 (125):2·9 | 336 (111):25·2** | 285 (90):26·4 | 51 (21):20·2 |
| | Total | | 115 (241):4·0 | 610 (233):21·8** | 511 (181):23·5 | 99 (52):15·9 |
| In past three months | Men | 57 | 404 (116):5·9 | 884 (122):12·3** | 769 (91):14·3 | 115 (31):6·3 |
| | Women | 59 | 540 (125):7·3 | 1218 (111):18·6** | 1056 (90):19·9 | 162 (21):13·1 |
| | Total | | 944 (241):6·6 | 2102 (233):15·3** | 1825 (181):17·1 | 277 (52):9·0 |

*p < 0·01 *v* controls.
Values in the table are number of affirmative answers (number of subjects):percentage prevalence.

*Table 3 Frequency distribution of subjective symptoms*

| Subjective symptoms | Sex | Controls | | | | Exposed | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | I | II | III | VI | I | II | III | IV |
| During work | Men | 85 | 22 | 9 | 0 | 23 | 74 | 19 | 6 |
| | Women | 104 | 17 | 4 | 0 | 18 | 52 | 26 | 15 |
| | Total | 189 | 39 | 13 | 0 | 41 | 126 | 45 | 21 |
| In past three months | Men | 20 | 91 | 5 | 0 | 13 | 83 | 18 | 8 |
| | Women | 16 | 97 | 12 | 0 | 6 | 55 | 36 | 14 |
| | Total | 36 | 188 | 17 | 0 | 18 | 138 | 54 | 22 |

p < 0·01 by $\chi^2$ test in all cases.
Values in the table are number of persons; categories I, II, III, and IV were 0, 1–3, 4–6, and 7 or more symptoms during work, and 0, 1–10, 11–20 and 21 or more symptoms in past 3 months.

*Table 4 Symptoms with significant difference (p < 0·01) in percentage prevalence (%) for men and women combined*

| Code No Symptom | Control (C) | Exposed (E) | E/C |
|---|---|---|---|
| During work: | | | |
| 1 Eye irritation | 6·2 | 28·6 | 4·6 |
| 2 Dimmed vision | 3·1 | 22·2 | 7·2 |
| 3 Nasal irritation | 8·3 | 28·2 | 3·4 |
| 5 Sore throat | 5·2 | 40·2 | 7·7 |
| 6 Unusual taste | 0·4 | 14·2 | 35·5 |
| 7 Face flashing | 2·1 | 8·6 | 4·1 |
| 8 Dizziness | 2·8 | 14·1 | 5·0 |
| 9 Floating sensation | 7·9 | 55·1 | 7·0 |
| 11 Heavy feeling in the head | 2·4 | 14·1 | 5·9 |
| 12 Headache | 6·9 | 32·9 | 4·8 |
| In the past 3 months: | | | |
| 4 Nausea | 8·6 | 26·5 | 3·1 |
| 6 Difficulty in sleeping | 18·2 | 38·5 | 2·1 |
| 7 Nightmare | 13·8 | 28·2 | 2·0 |
| 13 Forgetfulness | 16·8 | 42·7 | 2·5 |
| 14 Inability to concentrate | 3·4 | 18·0 | 5·3 |
| 18 Fainting after sudden standing up | 27·5 | 50·9 | 1·9 |
| 19 Palpitation | 11·0 | 26·9 | 2·4 |
| 24 Poor appetite | 3·8 | 16·7 | 4·4 |
| 26 Dry mouth | 7·9 | 39·7 | 5·0 |
| 51 Rough skin | 2·4 | 21·4 | 8·9 |

Code for each symptom is as in Yin *et al.*[25]

*Table 5 Comparison of haematology and serum biochemistry values*

| Item (Unit) | Men | | Women | |
|---|---|---|---|---|
| | Exposed | Controls | Exposed | Controls |
| No of subjects | 116 | 122 | 125 | 111 |
| Haematology: | | | | |
| Haemoglobin (g/100 ml) | 14·8 (1·1) | 14·8 (1·3) | 12·7 (1·5) | 12·5 (1·1) |
| Leucocytes ($\times 10^3$/mm$^3$) | 6·70 (1·76) | 6·46 (1·65) | 6·31 (1·63) | 6·34 (1·73) |
| Serum biochemistry: | | | | |
| Total protein (g/100 ml) | 7·35 (0·51) | 7·34 (0·40) | 7·54 (0·53) | 7·48 (0·46) |
| Total bilirubin (mg/100 ml) | 0·57 (0·29)* | 0·67 (0·47) | 0·51 (0·26)* | 0·57 (0·29) |
| γ-GTP (IU/l) | 8·8 (1·60)* | 10·2 (1·69) | 5·9 (1·70) | 6·4 (1·75) |
| ASAT (IU/l) | 22·5 (1·38) | 21·5 (1·41) | 18·8 (1·38) | 18·7 (1·38) |
| ALAT (IU/l) | 23·9 (1·77) | 22·1 (1·94) | 15·4 (1·84) | 14·7 1·83) |
| ALP (IU/l) | 260 (1·39) | 254 (1·34) | 202 (1·37) | 206 (1·35) |
| LAP (IU/l) | 48·9 (1·21) | 47·1 (1·15) | 42·1 (1·17) | 41·2 (1·17) |
| Creatinine (mg/100 ml) | 0·90 (0·12)* | 0·87 (0·11) | 0·71 (0·12)** | 0·66 (0·09) |

*p < 0·05, **p < 0·01.
Values for haemoglobin, leucocytes, total protein, total bilirubin and creatinine are arithmetic mean (ASD), whereas those for γ-GTP, ASAT, ALAT, ALP, and LAP are geometric mean (GSD) with assumptions of normal and log normal distributions, respectively.

## Results

PREVALENCE OF SUBJECTIVE SYMPTOMS

Table 2 shows that the prevalence of symptoms during work was significantly (p < 0·01) higher in the exposed than in the control group regardless of sex. This was also true for the prevalence of the symptoms in the past three months. As the response to two questions related to menstruation did not differ between exposed and control groups, the two sexes were combined after the exclusion of these questions.

When both exposed and non-exposed subjects were classified by the number of symptoms per person, the frequency distribution was significantly (p < 0·01) different for both symptoms during work and in the past three months (table 3).

Table 4 gives prevalences for each symptom with a significant increase (p < 0·01) in the exposed population. Most of the symptoms during work related depressive effects on the central nervous system (such as codes 9 and 11) or local irritation (codes 1, 3, and 5), whereas those in the past three month period were less specific. The exposed to control ratio (E/C) ranged from 35·5 to 3·4 for the work period and 8·9 to 1·9 for the past three months and was significantly higher (p < 0·05 by U test) in the work period than in the past three months.

For the detection of possible dose dependency, exposed workers were classified into two subgroups by exposure intensities of 1 to 20 ppm and 21 ppm or more. Comparison of prevalences indicated no dose dependent increase either during work or in the past three months (table 2).

HAEMATOLOGY AND SERUM BIOCHEMISTRY

Table 5 shows the results of haematology and serum biochemistry tests. Because haemoglobin concentrations are known to be different in the two sexes the findings were treated separately for men and for women. Differences between exposed and control groups were not significant for most of the items, and none of the statistically significant differences were clinically relevant.

## Discussion

The health examination of 233 Chinese solvent workers occupationally exposed to a mixture of toluene and three xylene isomers at low concentrations and 241 controls showed that the prevalences of some subjec-

tive symptoms were significantly increased in the study population. The symptom profiles were similar to those found after occupational exposure to toluene[18] or xylenes,[19] and focused on depression of the central nervous system and local irritation. In agreement with other observations,[26 27] haematology and serum biochemistry did not show noteworthy changes: this was also the case for workers exposed to toluene[18] or xylenes.[19]

The toxicity profiles are essentially the same for toluene, xylenes, and the mixture of the two, the central nervous system being the primary target. This suggests that it is justified when evaluating the toxicity of mixtures of toluene and xylenes at such low levels of occupational exposure, to add the effects.[20] The current occupational exposure limits for toluene and three xylene isomers are set at 100 ppm[20–22] indicating that their potencies are essentially equal in their ability to depress the central nervous system.

We thank Professor C Jin of the Institute of Occupational Medicine, Chinese Academy of Preventive Medicine, Beijing, China, Professor T Suzuki (the former Director), and Professor K Yoshinaga of Tohoku Rosai Hospital, Sendai 980, Japan for their support to this study.

1 Inoue T, Takeuchi Y, Hisanaga N, Ono Y, Iwata M, Ogata M, *et al.* A nationwide survey on organic solvent components in various solvent products: Part I. Homogeneous products such as thinners, degreasers and reagents. *Ind Health* 1983;**21**:175–83.
2 Kumai M, Koizumi A, Saito K, Sakurai H, Inoue T, Takeuchi Y, *et al.* A nationwide survey on organic solvent components in various solvent products: Part II. Heterogeneous products such as paints, inks and adhesives. *Ind Health* 1983;**21**:185–97.
3 Seedorf L, Olsen E. Exposure to organic solvents—I. A survey on the use of solvents. *Ann Occup Hyg* 1990;**34**:371–8.
4 Ogata M, Takatsuka Y, Tomokuni K. Excretion of hippuric acid and *m*- or *p*-methylhippuric acid in the urine of persons exposed to vapours of toluene and *m*- or *p*-xylene in an exposure chamber and in workshops, with specific reference to repeated exposures. *Br J Ind Med* 1971;**28**:382–5.
5 Kurppa K, Husman K. Car painters' exposure to a mixture of organic solvents. Serum activities of liver enzymes. *Scand J Work Environ Health* 1982;**8**:137–40.
6 Iregren A. Effects on psychological test performance of workers exposed to a single solvent (toluene)—A comparison with effects of exposure to a mixture of organic solvents. *Neurobehaviour Toxicology and Teratology* 1982;**4**:695–701.
7 Lungberg I, Hakkansson M. Normal serum activities of liver enzyme in Swedish paint industry workers with heavy exposure to organic solvents. *Br J Ind Med* 1985;**42**:596–600.
8 Jonai H, Sato M. Exposure indices for painters exposed to toluene and xylene at low concentrations. *Ind Health* 1988;**26**:197–202.
9 Sakai T, Takeuchi Y, Ikeya Y, Araki T, Ushio K. Method for simultaneous determination of six metabolites of toluene, xylene and ethylbenzene, and its application to exposure monitoring of workers in a printing factory with gravure machines. *Japanese Journal of Industrial Health* 1989;**31**:9–16. (In Japanese with English abstract.)
10 Cho B-M. Urinary concentration of hippuric acid and methylhippuric acid after occupational exposure to toluene and xylene. *Journal of Pusan Medical College* 1989;**29**:109–19. (In Korean with English abstract.)
11 Chen JD, Wang JD, Jang JP, Chen YY. Exposure to mixtures of solvents among paint workers and biochemical alterations of liver function. *Br J Ind Med* 1991;**48**: 696–701.
12 Hajimiragha H, Ewers U, Brockhaus A, Boettiger A. Levels of benzene and other volatile aromatic compounds in the blood of non-smokers and smokers. *Int Arch Occup Environ Health* 1989;**61**:513–8.
13 Chan C-C, Spengler JD, Ozkaynak H, Lefkopoulou M. Commuter exposures to VOCs in Boston, Massachusetts. *J Air Waste Manage Assoc* 1991;**41**: 1594–600.
14 Huang M-H, Jin C, Liu Y-T, Li B-H, Qu Q-S, Uchida Y, *et al.* Mixed exposure of workers to toluene and xylenes. I Metabolism. *Occup Environ Med* 1994;**51**:42–6.
15 Hirayama T, Ikeda M. Applicability of carbon felt to the dosimetry of solvent vapor mixture. *Am Ind Hyg Assoc J* 1979;**40**:1091–6.
16 Ikeda M, Kumai M, Aksoy M. Application of carbon felt dosimetry to field studies distant from analytical laboratory. *Ind Health* 1984;**22**:53–8.
17 Kasahara M, Ikeda M (1987) Spontaneous desorption of organic solvents from carbon cloth. *Ind Health* 1987; **25**:73–81.
18 Ukai H, Watanabe T, Nakatsuka H, Satoh T, Liu S-J, Qiao X, *et al.* Dose-dependent increase in subjective symptoms among toluene-exposed workers. *Environ Res* 1993;**60**:274–89.
19 Uchida Y, Nakatsuka H, Ukai H, Watanabe T, Liu Y-T, Huang M-Y, *et al.* Symptoms and signs of workers exposed predominantly to xylenes. *Int Arch Occup Environ Health* 1993;**64**:597–605.
20 American Conference of Governmental Industrial Hygienists. *Threshold limit values and biological exposure indices for 1992–1993.* Cincinnati: ACGIH, 1992.
21 Deutsche Forschungsgemeinschaft. Maximum concentrations at the workplace and biological tolerance values for working materials 1992. Weinheim: VCM, 1991.
22 Japan Association of Industrial Health. Recommended occupational exposure limits. *Japanese Journal of Industrial Health* 1992;**34**:363–84. (In Japanese.)
23 Liu SJ, Qu Q-S, Xu X-P, Liu Y-T, Yin S-N, Takeuchi Y, *et al.* Toluene vapor exposure and urinary excretion of hippuric acid among Chinese workers. *Am J Ind Med* 1992;**22**:313–23.
24 Inoue T. A table of subjective symptom questionnaires for solvent workers. In: *Japan Industrial Safety and Health Association Health management of solvent workers.* Tokyo: Japan Industrial Safety and Health Association, 1983: 66–67.
25 Yin S-N, Li G-L, Hu Y-T, Zhang X-M, Jin C, Inoue O, *et al.* Symptoms and signs of workers exposed to benzene, toluene or the mixture. *Ind Health* 1987;**25**: 113–30.
26 Browning E. Toluene, and xylene. In: *Toxicity and metabolism of industrial solvents.* Amsterdam: Elsevier, 1965: 66–89.
27 Antti-Poika M, Kalliokowski P, Hänninen O. Toluene. In: Snyder R, ed. *Ethyl Browning's toxicity and metabolism of industrial solvents.* Amsterdam: Elsevier, 1987: 36–63.
28 Riihimäki V, Pfäffli P, Savolainen K, Pekari K. Kinetics of m-xylene in man. General features of absorption, distribution, biotransformation and excretion in repetitive inhalation exposure. *Scand J Work Environ Health* 1979;**5**:217–31.