Title	A survey of urinary hippuric acid and subjective symptoms among occupational low toluene exposed workers
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Citation	Fukushima Journal of Medical Science. 49(2): 129-139
Issue Date	2003-12
URL	http://ir.fmu.ac.jp/dspace/handle/123456789/144
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DOI	10.5387/fms.49.129
Text Version	publisher

Fukushima J. Med. Sci.,
Vol. 49, No. 2, 2003
[**Original Article**]

A SURVEY OF URINARY HIPPURIC ACID AND SUBJECTIVE SYMPTOMS AMONG OCCUPATIONAL LOW TOLUENE EXPOSED WORKERS

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(Received August 6, 2003, accepted October 1, 2003)

Abstract: Biological monitoring of toluene exposure by urinary hippuric acid determination and a subjective symptom survey by self-administered questionnaire were performed in 20 workers at low toluene exposure in factories to evaluate the health hazard including dysfunction of nervous system. Environmental monitoring was carried out using toluene gas detection tubes. Urine samples were collected three times a day in order to measure hippuric acid: first before the commencement of work, then at the end of forenoon work, and lastly at the end of afternoon work. Toluene vapor concentrations of throughout the workday ranged from 15.3 to 31.4 ppm. The urinary hippuric acid concentrations correlated with the toluene concentrations of ambient air ($r=0.58$, $p=0.01$). The subjective symptoms increased in close association with the exposure to toluene; the prevalence rate of subjective symptoms "during work" in the exposed group was 15 times higher than the rate of the non-exposed group ($p<0.0001$). The prevalence rate of subjective symptoms "off-work" in the exposed group was 2.4 times higher than the rate of the non-exposed group ($p<0.0001$), and also the prevalence rate of "nineteen symptoms off-work which are apparently related to central nervous system (CNS) and autonomic nervous system (ANS)" in the exposed group was 1.8 times higher than the rate of the non-exposed group ($p<0.05$). From these results, these subjective symptoms, which have been believed to be complained in high organic solvent exposure should be reassessed and reconsidered in evaluating the nervous system dysfunction and local irritation in relatively low toluene exposed workers.

Key words: occupational exposure, low exposure, toluene, urinary hippuric acid,

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subjective symptoms.

INTRODUCTION

Toluene is a substance used extensively in industrial applications. It is known that toluene is toxic to the nervous system and may increase prevalence of subjective symptoms such as headache, insomnia, irritation and so on, categorized[1] as dysfunction of CNS or ANS among exposed workers[2,3,4]. Such deficits have been reported to occur when air concentrations of toluene is relatively high, over 50 ppm[5,6]. Recently low toluene exposure is paid attention in relation to sick building syndrome[7,8]. In order to prevent health degradation from harmful substance, it should be necessary to carry out such an assessment, even if the exposure level is relatively low.

In the Industrial Safety and Health Law in Japan, urinary hippuric acid, toluene's principal metabolite, is adopted as a biomarker in characterizing exposure-response relationships in order to evaluate working environment and working method. However, urinary hippuric acid seems to be unsuitable today as the estimator of exposure-response relationship or nervous system abnormalities, by reason why toluene concentration in the working air is decreasing due to improvement in working environments[9]. It is considered that subjective symptoms both of "during work" and "off-work" periods provide important information for the health care of solvent-exposed workers. The present study was initiated to elucidate the possibility of the exposure-effect monitoring in workers exposed to low toluene level in terms of subjective symptom prevalence.

METHODS

The practical research involved in this study was conducted in two chemical lacquer-ware manufacturing factories (A, B) in the Aizu region of Fukushima Prefecture in Japan from March to April in 1999, and was conducted during the second half of the working week (on Thursday and Friday). The Aizu district is known for its lacquer-ware production since ancient times. By following traditional lacquer-ware production technology, present-day workers of the factories have been performing surface-coating using chemical coating material on tableware made of plastic. During the manufacturing process, they use painting liquid which has the pigment dissolved in toluene solution, etc. Examined subjects comprised of 20 toluene-exposed workers and, as control, 9 non-exposed workers in these chemical lacquer-ware factories. Since these factories were small-scale enterprise, employee numbers totaled 29 persons. The exposed employees mainly worked as spray-painters or worked as their assistants. The control subjects were desk workers and were not exposed to toluene. For the most part, these workers' jobs

Table 1. Characteristics of subjects

		Non-exposed workers			Exposed workers		
		Total (n=9)	Male (n=3)	Female (n=6)	Total (n=20)	Male (n=12)	Female (n=8)
•Age (yeas old)		44.7 (13.9)	45.0 (11.4)	44.5 (15.0)	43.8 (13.3)	38.8 (11.1)	51.1 (12.8)
•Employment/Exposure to toluene (year)		9.4 (14.7)	15.7 (18.0)	6.3 (11.5)	13.3 (12.6)	14.5 (12.7)	11.5 (12.2)
•Alcohol drinkers (persons)	everyday	4	2	2	5	5	0
	2 days/week	0	0	0	1	0	1
	≦1 day/week	1	0	1	7	3	4
•Non-drinkers (persons)		4	1	3	7	4	3
•Smokers (persons)	5cigarettes/day	0	0	0	1	0	1
	6～10 /day	2	1	1	1	1	0
	11～20 /day	2	2	0	6	6	0
	21～30 /day	0	0	0	1	1	0
•Non-smokers (persons)		5	0	5	11	4	7

Mean (SD)

have been fixed since commencing employment at the factories.

The sex, age, smoking and drinking habits of the subjects are shown in Table 1. On the result of the statistical analysis as described below, the statistical significance was observed on age, employment years, and the number of the cigarettes per day using the Mann-Whitney U-test. The statistical significance on sex ratio, drinking habit and smoking habit was observed using the Chi-square-test. On sex ratio, age, and employment years, no significant difference was observed between exposed workers and non-exposed workers. There were no significant differences on age and employment period within each group. The proportion of current alcohol drinkers was significantly higher among the exposed male workers than among the exposed female workers ($p<0.05$). However, the actual consumption habits of alcohol drinkers (recorded in categories ranging from "every day" to "less than one day per week") were not significantly different between the sexes in the exposed and non-exposed groups. The prevalence of smoking was higher among the male workers than among the female workers in each group, and the number of cigarettes smoked per day was significantly higher among the male workers than among the female workers in each group (non-exposed group: $p<0.01$, exposed group: $p<0.05$). During work, none of the exposed workers were wearing gas masks or protective gloves. Three males among the exposed workers wore cotton gloves.

Environmental monitoring was carried out using a toluene gas detection tube (GASTEC, No. 122, GASTEC Corporation, Japan) every 30 minutes during working hours. Air samples were taken near the areas where spray guns were used. Other solvents mixed with toluene (such as butyl-acetate, ethyl-acetate, methanol, and metyl-ethyl-ketone) were measured using solvent-specific gas detection tubes (GAS-

TEC, butyl-acetate: No. 1421, ethyl-acetate: No. 1411, methanol: No. 111LL, metyl-ethyl-keton: No. 152) like the toluene measurement. For the environmental monitoring of the non-exposed workshops in both factories, only toluene was measured, using the same gas detection tube, once in the morning and once in the afternoon.

In order to exclude the influence of outside factors on the measurement of urinary hippuric acid, the subjects were instructed to finish dinner by 9:00 PM on the day before the examination. And alcohol drinking and consuming soft drinks were prohibited from 9:00 PM on the day before the examination until the end of work on the examination day. The subjects were ordered to excrete and discard their urine, immediately upon arrival to their factories and just before the beginning of afternoon work. Urine samples were collected three times for the measurement of hippuric acid, first before work (no toluene exposure), then at the end of forenoon work, and lastly at the end of afternoon work. These specimens were quickly frozen, and then preserved until quantitative measurement could take place. Quantitative measurement was undertaken 3 weeks after sampling. The hippuric acid concentrations of the urine specimens were measured by high performance liquid chromatography with UV absorptiometric analysis[10].

The authors employed Inoue's self-administered questionnaire[1] in order to survey the workers' subjective symptoms. This questionnaire has been used in the high level exposure of organic solvent, but it covers any symptoms of toluene exposure. The subjects were requested to complete a questionnaire evaluating their symptoms during work (12 questions) and their symptoms off-work over the preceding three months (54 questions). The prevalence rate of subjective symptoms was calculated as:

$$\frac{\text{number of affirmative answers by the group}}{(\text{number of the workers in the group}) \times (\text{number of questions})} \times 100(\%)$$

And the individual complaint rate was calculated as:

$$\frac{\text{individual number of affirmative answers}}{\text{number of questions in the symptoms during work and the like}} \times 100(\%)$$

After hearing an explanation of the details of the present study and having their privacy guaranteed by the authors, all subjects signed an informed consent form.

For statistical analyses, Mann-Whitney U-test, Chi-square-test, Fishers exact test and One-way-analysis of Variance were performed using SPSS Version 9.0 (SPSS Inc., Chicago, IL, USA). Statistical significance for analyses was set at p-value 0.05.

RESULTS

The toluene concentrations of ambient of workshops

The toluene concentrations as 8-hour TWA (time-weighted average of the total working hours) from the exposed workshops in both factories ranged from 15.3 to

Table 2. Toluene levels of ambient air in workshops monitored during the complete working hours.

	Working hours (h)			Work-shops	Toluene concentration in air (ppm)		
	fore-noon	after-noon	total		8 hour TWA (over total working hours)	hightest concentration forenoon	afternoon
Factory A	3	5	8	A^1	23.5	25	50
				A^2	15.3	22	25
				A^3	16.9	23	25
				A^4	0	—	—
				A^5	0	—	—
Factory B	4	4	8	B^1	31.4	40	45
				B^2	24.6	45	30
				B^3	18.1	20	30
				B^4	18.0	10	50
				B^5	0	—	—

TWA : time-weighted average.
A^1, A^2, A^3, B^1, B^2, B^3 and B^4 : Workshops using toluene.
A^4, A^5, B^5 : Workshops for desk work and packaging work.

31.4 ppm. These TWA were less than 50 ppm, the threshold limit set by the Japan Society for Occupational Health. Toluene was not detected in the non-exposed workshops of either factory (Table 2). The TWA of other minor solvents butyl-acetate and ethyl-acetate were ranging from 12.5 to 25.6 ppm and ranging from 3.1 to 6.3 ppm, respectively in both factories. These concentrations were extremely low comparing to each threshold limit by Japan Society for Occupational Health (butyl-acetate, 100 ppm ; ethyl-acetate, 200 ppm). The concentrations of other minor solvents were low levels from each detection limits.

Urinary hippuric acid

In order to evaluate the toluene exposure, urinary hippuric acid was measured. Fig. 1 shows the urinary hippuric acid concentrations of the exposed and the non-exposed workers. The urinary hippuric acid concentration of non-exposed workers was 0.12 ± 0.11 g/l (mean$\pm$SD) at the beginning of their work, 0.10 ± 0.07 g/l at the end of forenoon work and 0.07 ± 0.06 g/l at the end of afternoon work. Those of the exposed workers was 0.23 ± 0.31 g/l at the beginning of their work, 0.32 ± 0.28 g/l at the end of forenoon work and 0.47 ± 0.38 g/l at the end of afternoon work. At the end of afternoon work, the exposed workers' hippuric acid was significantly higher than that of the non-exposed workers at the same period ($p < 0.0001$).

The concentrations of urinary hippuric acid in the exposed workers at the end of forenoon work and the end of afternoon work were significantly higher than those noted at the beginning of work ($p < 0.05$). And there were significant positive correlations between the toluene $TWA_{3or4-hour}$ (during forenoon work) of ambient air and concentration of hippuric acid at the end of forenoon work ($r = 0.52$, $p < 0.05$),

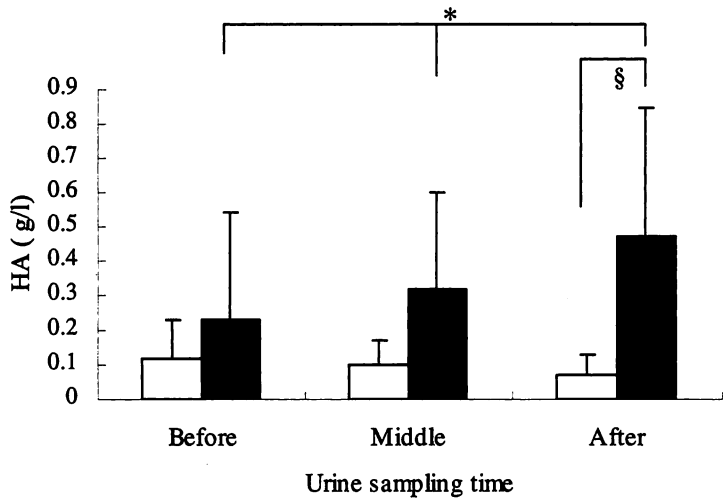

Fig. 1. Changes in urinary hippuric acid in exposed and non-exposed workers. Values are mean±SD. Statistical significance was observed by Mann-Whitney U test and ANOVA. §: $p<0.0001$, (non-exposed VS exposed workers). *: $p<0.05$, $F=5.85$, (exposed workers). Urine sampling time: Before means before of beginning of work, Middle means at the end of forenoon work, and After means at the end of afternoon work. Open columns are for the non-exposed workers and black ones are for the exposed workers.

and between the toluene $TWA_{8\text{-hour}}$ (during complete work) of ambient air and concentration of hippuric acid at the end of afternoon work ($r=0.58$, $p=0.01$). So, in the exposed workers, it was shown that there was the exposure-absorption relationship.

Survey of subjective symptoms

Table 3 indicates the subjective symptoms that occurred during work and off-work in the past three month in each group. The workers complained of 9 of 12 symptoms during work, and 46 of 54 symptoms off-work. The difference in the prevalence between the exposed group and the non-exposed group was significant for only "thirst" symptoms ($p=0.026$). Whereas, it is evident the prevalence rate of subjective symptoms during work was 13.8% in the exposed group, higher than the rate of the non-exposed group (0.9%), ($p<0.0001$), and the prevalence rate of subjective symptoms off-work was 14.4% in the exposed group, higher than the rate of the non-exposed group (6.0%), ($p<0.0001$), and also the prevalence rate of nineteen symptoms during off-work (Table 3, marked with ○) which are apparently related to CNS and ANS was 16.8% in the exposed group, higher than the rate of the non-exposed group (9.4%), ($p<0.05$). Regarding the association between the observed increase in complaint rate of subjective symptom and toluene level of ambient air (Fig. 2), the exposed workers were sub-grouped depending on the intensity of their ambient toluene into those with <20 ppm ($n=6$), 20≦ to <24 ppm ($n=9$), and ≧24

Table 3. Prevalence rate of symptoms during work and off-work in the past three months among non-exposed workers and exposed workers.

Subjective symptoms	Non-exposed workers $n=9$		Exposed workers $n=20$	
	A.A.*1 (the number)	Prevalence-rate*2 (%)	A.A. (the number)	Prevalence-rate (%)
•During work				
Offensive smell	0	0	7	35
Nasal irritation	0	0	5	25
Difficulty seeing	0	0	4	20
Irritation in throat	0	0	4	20
Eye irritation	0	0	3	15
Feeling of drunkenness	0	0	3	15
Heaviness in head	0	0	3	15
Headache	1	11	3	15
Offensive taste	0	0	1	5
prevalence rate as a whole (: 12 symtoms)§§		0.9		13.8
•Off-work in the past three months				
Thirst*	0	0	8	40
○Headache	2	22	7	35
○Insomnia	1	11	7	35
○Irritation	1	11	7	35
Difficulty seeing	1	11	7	35
○Heaviness in head	0	0	6	30
Skin abnormalities	1	11	6	30
○Lapse in memory	1	11	5	25
Poor digestion	2	22	5	25
○Eyestrain	2	22	5	25
Pain in upper or lower limbs	0	0	5	25
○Anxiety	0	0	4	20
○Inability to concentrate	1	11	4	20
Tightness in chest	1	11	4	20
Weariness	0	0	4	20
Paralysis of upper or lower limbs	1	11	4	20
Decrease in grasping power	0	0	4	20
Decrease in hand and foot strength	0	0	4	20
Stumbling	1	11	4	20
Throat abnormality	0	0	4	20
Cough	0	0	4	20
Gingival hemorrage	0	0	4	20
○Nausea	2	22	3	15
Difficulty breathing	0	0	3	15
Poor appetite	0	0	3	15
Abdominal pain	0	0	3	15
○Ringing in ears	0	0	3	15
○Vertigo	0	0	2	10
○Unsteady feeling	0	0	2	10
Dizziness when standing	1	11	2	10
Tachycardia	1	11	2	10

(Continue)

Table 3. Continued.

Subjective symptoms	Non-exposed workers $n=9$		Exposed workers $n=20$	
	A.A.[#1] (the number)	Prevalence-rate[#2] (%)	A.A. (the number)	Prevalence-rate (%)
Heaviness in limbs	0	0	2	10
Diarrhea	1	11	2	10
Constipation	2	22	2	10
○Decrease in sexual appetite	1	11	2	10
○Unable to hear properly	1	11	2	10
Coldness in hands and feet	0	0	2	10
○Easily intoxicated	1	11	2	10
○Unable to keep food down	1	11	1	5
○Nightmares	0	0	1	5
○Fuzziness in head	1	11	1	5
Weightloss	0	0	1	5
Slight fever	0	0	1	5
Abnormal perspiration	0	0	1	5
Unable to express self well	1	11	1	5
○Spasms	1	11	0	0
prevalence rate as a whole (: 54 symtoms)§§		6.0		14.4
prevalence rate as a whole (: 19symtoms marked with○)§		9.4		16.8

[#1]: affirmative answers. [#2]: Prevalence rate of symptoms is defined in method.
○: subjective symptoms from dysfunction of both central and autonomic nervous system.
*: $p<0.05$, Fishers exact test, §§: $p<0.0001$, §: $p<0.05$, unpaired t-test.

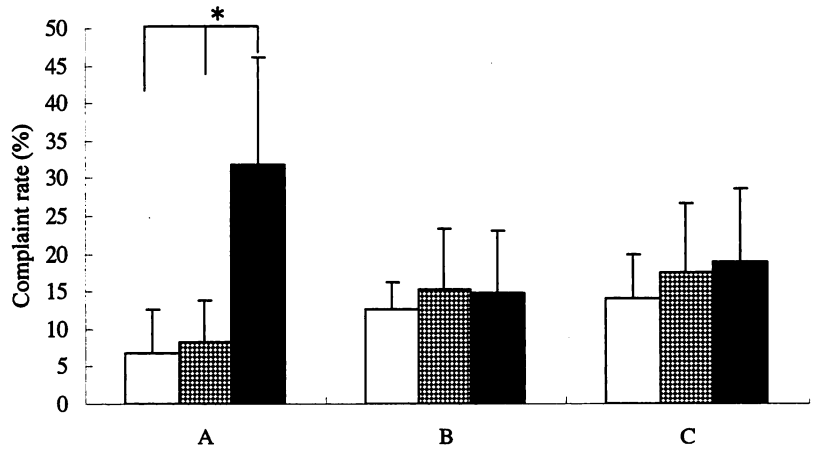

Fig. 2. Complaint rate of symptoms by toluene levels of ambient air.
Values are mean±SD. Complaint rate of symptoms is defined in method. Exposed group was classified into those ambient toluene levels at <20 ppm ($n=6$), Open columns; 20≦～<24 ppm ($n=9$), Dotted ones; ≧24 ppm ($n=5$), Black ones. A, the 12 questions on symptoms during work; B, the 54 questions on symptoms off-work; C, the 19 questions on symptoms relate to CNS and ANS effects. CNS, central nervous system; ANS, autonomic nervous system. *$p<0.01$, ANOVA.

ppm ($n=5$). The Complaint rate of subjective symptoms during work stays rather unchanged up to 24 ppm exposure. The complaint rate in the $\geqq 24$ ppm group was significantly higher than those noted in the <20 ppm group and the $20\leqq$ to <24 ppm group ($p<0.01$).

DISCUSSION

Urinary hippuric acid has been considered a biomarker of exposure-response relationships, since it correlates better with high concentration of toluene exposure than that with low concentration. In 1995, the threshold limit for exposure to toluene set by the Japan Society for Occupational Health was lowered from 100 to 50 ppm. Urinary hippuric acid may be insufficient as an estimator of toluene exposure, due to improvements in working environments. In fact, in this survey, the toluene concentrations valued as 8-hour TWA were less than the 50 ppm, and among the exposed workers, individual urinary hippuric acid value at the end of afternoon work ranged from 0.06 to 1.58 g/l. Many of them were below 1.0 g/l, which is the normal level of the Industrial Safety and Health Law in Japan. The hippuric acid examination may make most of the exposed workers a negative in the specific health examination for toluene exposure. However, the exposed workers of this study seem to indicate some effects by the exposure-absorption of toluene, because they were complaining of the symptoms. In order to prevent health degradation from harmful substance, it is necessary to carry out such an assessment, even if the exposure levels are below the threshold limit, and their urinary hippuric acid levels are below the control level of the Industrial Safety and Health Law in Japan. In addition, it is described in the following, that in 1992 an international panel of experts recommended a threshold limiting value of 20 ppm of toluene in ambient air[11]. This recommendation was based on studies which demonstrated effects on the central nervous system and irritation of the mucus membranes at exposure to toluene higher than 40 ppm[12] and reproductive effects at exposures higher than 100 ppm[13] of toluene in ambient air.

Recently, increasing attention has been paid to the abnormalities in neurobehavioral function accompanying solvent exposure in the absence of obvious clinical disease[2,3,4]. Since 1940s, subjective symptoms have respected the interest of researchers of solvent toxicity. However, the ambient concentrations of workshops of that time were high levels such as 200 to 500 ppm or 500 to 1,500 ppm[14]. About reports considering the effects of toluene exposure at low levels, Matsusita *et al.*[15] reported anxiety as a complaint among workers exposed to toluene at 60-100 ppm, and also Larsen *et al.*[16] found a significantly greater prevalence of chronic mild encephalopathy among rotogravure workers exposed to toluene at 50-80 ppm for at least 12 years, Among workers exposed to toluene levels at 50-100 ppm, Ukai *et al.*[17] found that a dose-dependent increase in complaints occurred during and after toluene exposure.

The present study revealed that the subjective symptoms would increase in close association with toluene concentration of ambient air ranged from 15.3 to 31.4 ppm. The concentration of toluene was relatively low, compared with that of almost of the above reports. In the present study it is evident the prevalence rate of subjective symptoms during work in the exposed group was 15 times higher than the rate of the non-exposed group. And dose dependency of increase in prevalence was observed about the subjective symptoms during work. The prevalence rate of subjective symptoms off-work in the exposed group was 2.4 times higher than the rate of the non-exposed group, and also the prevalence rate of nineteen symptoms off-work which are apparently related to CNS and ANS in the exposed group was 1.8 times higher than the rate of the non-exposed group. Thus, toluene exposure appeared to be associated with an increase in subjective symptoms during work. There is also a toluene-associated increase in the subjective symptoms off-work but the increment over the non-exposed group levels is not as large as that of during work. Prior to the investigation, the authors explained the purpose of this study to the subjects. Since the subjects were made aware of our hypothesis on the health hazard effect by toluene, the possibility of this affecting their symptoms complaint situation may be a criticism to be indicated. However, as these organic solvent workers have experienced the specific health examination for them since their employment, they would have already recognized the effect on their health by the toluene. Therefore any bias towards their symptoms complaint situation resultant from our prior explanation should be small.

Dose-response relation was not observed between ambient toluene level and the symptoms relating to CNS and ANS effects but between ambient toluene level and the symptoms during work. Although Inoue's self-administered questionnaire used in this study has been used in relatively high toluene concentration (over 100 ppm), it should be important to link these subjective symptoms with information of biological effect in order to make the health care of relatively low toluene exposed workers, even if the ambient toluene concentration or hippuric acid in urine is within limiting level.

ACKNOWLEDGMENT

The authors wish to gratefully thank Mr. Hideo Suzuki, Mr. Akio Hashiyada and Mr. Kazuhito Satoh, Department of Spray-Painting, Association of Aizu Lacquer Ware.

This study was supported by a research grant from the Fukushima Society of Medical Science, Fukushima, Japan.

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