

Exposure reconstruction of trichloroethylene among patients with occupational trichloroethylene hypersensitivity syndrome

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Abstract: Occupational trichloroethylene (TCE) exposure can induce life-threatening generalized dermatitis accompanied by hepatitis: TCE hypersensitivity syndrome (HS). Since the patients' exposure levels have not been fully clarified, this study estimated end-of-shift urinary concentrations of trichloroacetic acid (TCA) and their lower limit below which the disease occurrence was rare. TCA concentration was measured in 78 TCE HS patients whose urine was collected at admission between 2nd and 14th d after their last shift. Then a linear regression model was used to calculate the mean TCA concentration with 95% confidence interval (95% CI) and 95% prediction interval (95% PI) in the end-of-shift urine. The estimated mean concentration was 83 (95% CI, 49–140) mg/l with 95% PI 9.6–720 mg/l. TCA concentrations were also measured in the end-of-shift urine of 38 healthy workers involved in the same job as were the patients. The geometric mean and its 95% CI were 127 mg/l and 16–984 mg/l, respectively. The exposure levels in HS patients might have thus overlapped with those in workers without HS. Accordingly, it was suggested that HS occurred in the environment where the workers were exposed to the TCE concentration corresponding to the urinary TCA concentration as low as 10 mg/l.

Key words: Hypersensitivity syndrome, Occupational exposure, Prediction interval, Trichloroacetic acid, Trichloroethylene, Urine

Introduction

Trichloroethylene (TCE) is mainly used as an industrial solvent to remove grease from metal parts or lenses. Despite decreased usage in industrialized countries, its use has increased in Asian countries undergoing rapid

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industrialization. In these countries, life-threatening generalized dermatitis with hepatitis, which is internationally termed occupational TCE hypersensitivity syndrome (HS)¹ based on its pathophysiological characteristics, has recently received attention as an important TCE-induced occupational disease because its occurrence has increased remarkably in these countries since the mid-1990s^{1, 2}. The disease is characterized by clinical manifestations that are not typical of usual solvent intoxications, such as a huge difference in individual susceptibility to the disease, skin rash, hepatitis, fever, leukocytosis, lymphadenopathy, and human herpes virus 6 reactivation. These manifestations occur after occupational TCE exposure for an average duration of 1 month and correspond to those observed in drug-induced HS or drug reaction with eosinophilia and systemic symptoms, a disease entity involving severe adverse cutaneous reactions to drugs^{1, 3}. Importantly, two particular cases have been reported who refused to receive necessary medication, and died after returning to their workplaces^{4, 5}. Given that eight TCE HS cases have so far been reported in Japan^{2, 6-8}, the disease prevention should be taken into account not only in developing but developed countries.

Although the level of TCE exposure causing the disease is unclear, our previous studies have clearly demonstrated that patients with HS were exposed to high levels of TCE^{3, 9}. Specifically, the patients' exposure levels were determined from the urinary concentrations of trichloroacetic acid (TCA) as a TCE metabolite and were estimated to be mostly higher than 50 mg/l^{3, 9}, which is an Occupational Exposure Limit Based on Biological Monitoring (OEL-B) for TCE recommended by the Japan Society for Occupational Health¹⁰. However, the minimal exposure level that potentially causes the disease remains unclear. Notably, some patients might have suffered from HS despite having an exposure level below the OEL-B. Because this estimation was based on the case series approach using a previously reported biological half-life (BHL)¹¹, determining the exposure levels in TCE HS patients by means of a robust statistical method is an urgent need to prevent the disease.

Once absorbed in the body, TCE is metabolized through at least two pathways: a cytochrome P450 (CYP)-dependent oxidation pathway and a glutathione S-transferase-dependent conjugation pathway^{12, 13}. The former is saturated at a much lower concentration than the latter. The major metabolites, i.e., trichloroethanol (TCOH) glucuronide and TCA, are produced via chloral hydrate in the CYP-dependent pathway and are excreted into the urine. These

metabolites are often measured for biological monitoring. Given that the BHL of TCA is longer than that of TCOH, the former is usually used as a Biological Exposure Index (BEI) of TCE¹⁴.

The present study aimed to estimate the distribution of urinary TCA concentrations among patients suffering from occupational TCE HS and to estimate the lower limit of the TCE exposure level below which the disease occurrence was rare.

Subjects and Methods

Subjects

This study protocol was reviewed and approved by the Ethical Committee of the Nagoya University Graduate School of Medicine (No. 607), Nagoya City University Graduate School of Medical Sciences (No. 505), Chubu University (No. 240046), and the Guangdong Province Hospital for Occupational Disease Prevention and Treatment (GPHODPT). All subjects provided written informed consent. One hundred fifty Chinese patients with TCE HS [age: mean \pm standard deviation (SD), 23.6 \pm 6.6 yr] were admitted to GPHODPT between 2002 and 2008. The diagnosis of TCE HS was made according to the Chinese National Diagnostic Criteria of Occupational Medicamentosa-like Dermatitis due to Trichloroethylene (GBZ 185-2006)¹⁵. The diagnostic criteria required that the patients met all of the following conditions: suffering from any of the following rash phenotypes, i.e. exfoliative dermatitis, erythema multiforme or Stevens-Johnson syndrome/toxic epidermal necrolysis^{1, 3}, always accompanied by fever, liver dysfunction and superficial lymphadenopathy; having apparent occupational history of exposure to TCE; being exposed for 5-40 d in general or more, but not more than 80 d; and being only a fraction of workers under the same working environment where others worked without suffering from the disease¹⁵. All had used TCE during their work to degrease, clean, polish, or press metal materials or circuit boards, and the mean duration from the commencement of exposure to disease onset was 29.6 \pm 10.4 d. Most patients were transferred to GPHODPT from other hospitals to receive better intensive treatment or to apply for workers' compensation. Thus, the intervals between the last exposure and urine sampling varied (from 1 to >30 d) among the HS patients, although the urine samples were collected on the first day of hospitalization, in principle. In the present study, samples collected within 2 wk after the last day of exposure [n=78 (38 men and 40 women); age, 24.2 \pm 7.2 yr; Table 1] were analyzed

Table 1. Profiles of TCE HS patients and TCE-exposed workers without HS analyzed in the present study

	HS patients	Exposed workers without HS	Note
n (men, women)	78 (38, 40)	38 (27, 11)	†
Age (yr, mean ± SD), Total	24.2 ± 7.2	24.6 ± 6.8	
Men	25.3 ± 7.6	26.4 ± 6.9	
Women	23.1 ± 6.7	20.1 ± 4.3	
Disease-free exposure duration (d, mean ± SD), Total	28.5 ± 10.0	523 ± 568	†
Men	28.8 ± 12.1	662 ± 615	†
Women	28.2 ± 7.5	180 ± 178	†
Rash phenotype, n (men, women)			
Exfoliative dermatitis	42 (22, 20)	-	
Erythema multiforme	22 (9, 13)	-	
Steven-Johnson syndrome	4 (2, 2)	-	
Toxic epidermal necrolysis	6 (2, 4)	-	
Undiagnosed	4 (3, 1)	-	
Time interval after last TCE exposure until urine collection (d, mean ± SD), Total	7.6 ± 3.8	0 ± 0	†
Men	7.5 ± 3.7	0 ± 0	†
Women	7.7 ± 4.0	0 ± 0	†
Detected TCA concentrations in urine (mg/l, min–max), Total	0.7–216.8	9.9–1,617	
Men	2.0–216.8	9.9–1,617	
Women	0.7–216.1	20.8–404.6	
95% PI of end-of-shift TCA concentrations (mg/l, Model 1), Total	9.6–720	-	
End-of-shift TCOH concentration in urine [mg/l, geometric mean (min–max)], Total	ND	147 (21.5–1,804)	
Men	ND	194 (22.2–1,804)	
Women	ND	75 (21.5–303)	†

HS: hypersensitivity syndrome; ND: not determined; PI: prediction interval; TCA: trichloroacetic acid; TCE: trichloroethylene; TCOH: trichloroethanol. †Gender distribution, disease-free exposure duration, and time interval until urine collection were significantly different between the patient and the disease-free worker groups ($p < 0.05$).

for estimating urinary TCA concentrations at the end of shift. This selection criterion was based on our previous finding of a good correlation between log-transformed TCA concentrations and the duration after last exposure to TCE among patients whose urine was collected during this period⁹). All the rash phenotypes observed in TCE HS were noted in the selected patients. Disease-free exposure duration of TCE was clearly shorter in HS patients than that of healthy workers.

To clarify the actual TCE exposure levels among the workers without HS in the same workshops as the patients, TCA and TCOH concentrations were measured in the end-of-shift urine of 38 workers without HS (27 men and 11 women; age, 24.6 ± 6.8 yr; gender distribution was not matched with the patient group because of the limited number of available samples). These urine samples had been collected during our previous cross-sectional exposure survey of six factories where HS had occurred in the same year⁹). In that survey, the personal exposure concentrations of TCE were also monitored using diffusion samplers (Sibata Scientific Technology, Japan). The

geometric mean of 8-h time-weighted-average (TWA) concentrations was 165.4 mg/m³ (30.8 ppm at 25°C), with a range of 23.8–3,495 mg/m³ (4.4–650 ppm).

Measurement of TCA and TCOH in urine

Urine samples were stored at less than –30°C until analyses. The urinary TCA (assessed among both patients and healthy exposed workers) and TCOH [assessed only among healthy workers because of its short BHL compared with TCA^{14, 16}] concentrations were measured using a head-space gas chromatography equipped with an electron capture detector (GC-ECD; LSI Medience Corporation, Tokyo, Japan), as described previously^{9, 17}). This procedure was performed as per the quality control and quality assurance program of the National Federation of Industrial Health Organization, Japan. Creatinine concentrations in urine were measured by SRL Inc. (Tokyo, Japan).

Statistics

In order to estimate pharmacokinetic or toxicokinetic parameters, a population pharmacokinetic approach which

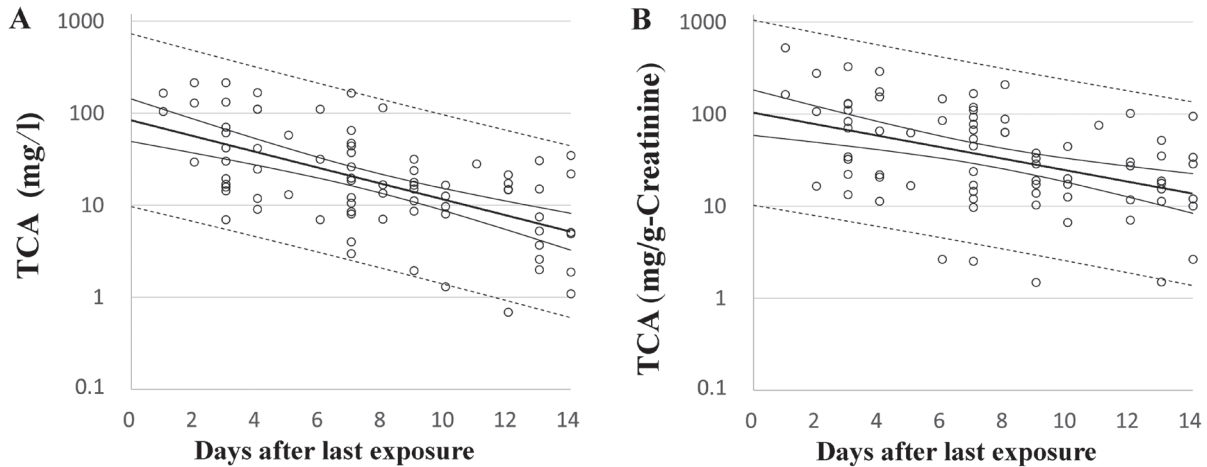


Fig. 1. Relationship between the interval (X, days) from the last TCE exposure to urine collection and TCA concentrations (Y) in patients suffering from TCE HS (n=78). The interval varied among the patients because they were not necessarily admitted to the hospital immediately after disease occurrence. Bold, fine and dotted lines represent the regression lines, its limits of 95% confidence interval and 95% prediction interval (PI), respectively. A. Before creatinine adjustment (Model 1). $Y \text{ (mg/l)} = 83.41 \times 10^{-0.086X}$ ($R^2 = 0.348$). PI of the TCA concentrations in the end-of-shift urine (Day 0) was estimated to be 9.6–720 mg/l; B. After creatinine adjustment (Model 2). $Y \text{ (mg/g creatinine)} = 103.36 \times 10^{-0.063X}$ ($R^2 = 0.197$).

uses a single blood sample from each patient can be adopted when conventional data from studies characterized by rigid and extensive sampling design are not available¹⁸). In the present study, since the sampling time after the cessation of exposure varied among the patients, and the present data set is sparse from the viewpoint of toxicokinetics, we adopted an approach in accordance with population pharmacokinetic studies. The objective of the present approach was to estimate the distribution of end-of-shift urinary TCA levels and the BHL of urinary TCA concentrations in TCE HS patient group in Guangdong Province, China. As an estimation process, first, a one-compartment model with first order elimination was fitted to the present data, based on the scatter plot of the data set (Fig. 1). Second, a multiple linear regression analysis was conducted between common log-transformed TCA concentrations (Y) as a dependent variable and the time interval from last exposure to urine collection (X) and possible covariates, i.e. age, sex, body weight as a surrogate parameter of volume of distribution, and liver function (alanine aminotransferase, ALT). Third, the end-of-shift concentrations were estimated for those without creatinine adjustment after removing non-significant covariates from the regression model. The conditional mean of the concentration when $X=0$ (Y-intercept) was calculated along with the 95% confidence interval (CI) and 95% prediction interval (PI) for actual Y, and the Y-intercept and lower limit of the 95% PI were regarded as the mean and lower limit values, respectively,

of observable end-of-shift urinary TCA levels. For the 38 healthy exposed workers, the Shapiro-Wilk normality test was used to examine the log-normality of the distribution of urinary TCA and TCOH concentrations. The geometric mean and its 95% CI were then calculated after log-normal distribution was ascertained.

Results

Urinary TCA levels in TCE HS patients

Table 1 shows the profiles of the HS patients. No significant differences in age ($p=0.16$), durations of exposure before disease onset ($p=0.76$), rash phenotypes ($p=0.69$), and time intervals from last exposure to urine collection ($p=0.82$) were observed between male and female patients (Student's *t*-test or Fisher's exact test). TCA was detected in urine samples from all patients (range, 0.7–216.8 mg/l; Table 1).

The measured urinary TCA levels of 78 patients were plotted against the time interval from last exposure to urine collection (Fig. 1A and B). A multiple linear regression analysis revealed that the time interval from last exposure to urine collection was significant in both Model 1 (for TCA concentrations before creatinine adjustment) and Model 2 (for the concentrations after the adjustment), while the following possible covariates, i.e., age, sex, body weight and ALT in Model 1 and age, body weight and ALT in Model 2, were not significant (Table 2). The

Table 2. Standardized partial regression coefficients (β) and 95% confidence interval (CI) between estimated urinary TCA concentration and independent variables

Variables	Model 1 ($R^2=0.366$)		Model 2 ($R^2=0.262$)	
	TCA (mg/l)		TCA (mg/g-Creatinine)	
	β	95%CI	β	95%CI
Time interval from last exposure to urine collection (d)	-0.592	-0.782, -0.402	-0.468	-0.673, -0.263
Sex (1: women, 2: men)	-0.129	-0.334, 0.076	-0.227	-0.448, -0.005
Age	0.072	-0.119, 0.264	0.020	-0.186, 0.227
Body weight (kg)	0.056	-0.152, 0.263	0.012	-0.211, 0.235
ALT [†] (U/l)	0.036	-0.154, 0.226	0.134	-0.071, 0.339

Model 1, a regression equation using TCA concentration before creatinine adjustment; Model 2, after the adjustment. [†]Common log-transformed values were used in the analysis.

end-of-shift concentrations were then estimated using only Model 1 by removing the non-significant covariates from the model. This is because of the fact that the coefficient of determination of Model 2 ($R^2=0.262$) was lower than that of Model 1 ($R^2=0.366$), that the end-of-shift TCA concentrations after creatinine adjustment in workers without HS were not log-normally distributed, and that American Conference of Governmental Industrial Hygienists (ACGIH) mentioned that the adjustment did not result in any significant improvement of correlation between levels of TCE exposure and urinary TCA¹⁴). The regression equation finally obtained was Y (mg/l)= $83.41 \times 10^{-0.086X}$ with $R^2=0.348$. The Y-intercept, 95% CI, and 95% PI were 83, 49–140, and 9.6–720 mg/l, respectively (Fig. 1A). Using these equations, the BHL of TCA was calculated to be 83.7 h. The model stability was then examined by an internal validation method¹⁸); a randomly sampled data subset ($n=52$, two-thirds of the data) was used for model building, and the remaining data subset ($n=26$) was used for model validation. The obtained equation was Y (mg/l)= $101.13 \times 10^{-0.100X}$ with $R^2=0.435$ (95% PI 12–870 for the Y-intercept). Ninety-two percentage patients (24/26) of the validation data set were actually distributed within their 95% PIs. It was thus confirmed that the model was statistically stable for estimating TCA concentration distribution, especially lower limit of PI, in the end-of-shift urine.

End-of-shift urinary TCA levels among TCE-exposed workers without HS engaged in six factories where HS occurred

The end-of-shift urinary TCA levels before creatinine adjustment in 38 workers without HS were log-normally distributed (Fig. 2). As for the levels after the adjustment they were not log-normally distributed (data not shown),

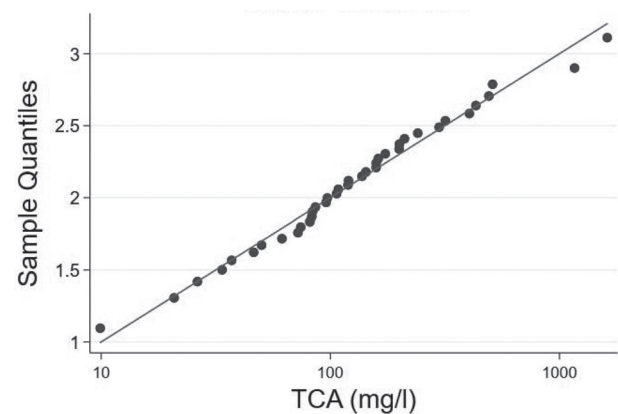


Fig. 2. Quantile-Quantile plot of common log-transformed end-of-shift urinary TCA concentrations (mg/l) in workers using TCE but not suffering from HS ($n=38$). The null hypothesis that the data was log-normally distributed was not rejected (Shapiro-Wilk test). Geometric mean and 95% confidence interval were 127 and 16–984 mg/l, respectively.

thereby making us decide not to use them for exposure assessment, which was in accordance with that ACGIH used urinary TCA concentration without creatinine adjustment as a Biological Exposure Index of TCE¹⁴). The geometric mean (95% CI), lowest value, and highest value of urinary TCA were 127 (16–984), 9.9 and 1,617 mg/l, respectively, and of TCOH were 147 (20–1,083), 21.5, and 1,804 mg/l, respectively. Gender difference was not significant in the geometric mean of TCA ($p=0.081$) levels, while significant in that of TCOH ($p<0.01$) (Student's *t*-test after log-transformation).

Discussion

Generally, TCA concentration in end-of-shift urine at the end of a workweek is most commonly used as a

biological monitoring index of TCE exposure because of its longer BHL compared with TCOH^{14, 16}). In the present study, TCA was detected in the urine of all HS patients even though they had quit their TCE-exposed work up to 2 wk before urine collection. This was the start point of our attempt to clarify TCE exposure levels in HS patients. The mean and 95% PI concentrations of TCA in the end-of-shift urine were estimated to be 83 mg/l and 9.6–720 mg/l, respectively.

Because the HS patients' actual end-of-shift urine was unavailable, we adopted a statistical approach in accordance with population pharmacokinetic studies¹⁸). In our approach, one-compartment model with first order elimination was assumed, and the minimum set of factors possibly contributing to toxicokinetic parameters was included in the initial models. The regression analyses and the validation results suggested that we could stably estimate the concentration distribution, especially lower limit of the 95% PI that is of our main interest, in the end-of-shift urine from the present data set. In this approach, the differences between the individual workers, e.g., TCE exposure levels and inherent enzyme activities that contributed to urinary TCA concentrations, which could deviate from the linear increase when the airborne TCE concentration exceeded 50 ppm¹⁶), were part of the residual variation in the regression model.

The calculated population BHL in HS patients (83.7 h) was longer than previously reported values [39.7 h in six male Japanese workers intermittently exposed to up to 200 ppm, 57.6 h in six female Japanese workers intermittently exposed to up to 50 ppm^{11, 16}), and 73 h in a 38-year-old Japanese men who habitually sniffed TCE soaked in a cloth up to three times a day¹⁶]. This difference might have resulted from the following factors. First, working hours were longer and the frequency of day off were less in general in the present population compared to the employment standards in the developed countries⁹), which might have resulted in the extensive accumulation of TCE and its metabolites in the body. This possibility was inferred from our previous data that the urinary TCA levels were not necessarily different between before and after a day off in the workers without HS⁹). Second, there might be an ethnic difference in TCE metabolism¹⁹): all our patients were Han Chinese. Third, it remains unknown whether the activity of a major oxidative enzyme of TCE, CYP2E1¹³), was comparable between the patients and healthy workers because almost all the patients suffered from severe hepatitis, which is a characteristic of TCE HS^{1, 3}); experimental evidence has however revealed that

the activity of CYP2E1 remained at the same level after hepatic damage was induced by TCE exposure in rats²⁰), and our results have shown that the liver function was not a significant contributing factor to the estimated TCA levels. Thus, it should be noted that the BHL as well as estimated concentrations in the present study might be different in other working populations under different TCE exposure control. This is why we did not estimate end-of-shift urinary TCA concentrations in the individual HS patients by using BHL reported by other authors.

There were additional uncertainties with regard to BHL in the HS patients. Although the patients' sex was not included in the final regression equation, Fisher²¹) used higher maximum reaction velocity, V_{max} , of TCE and higher urinary excretion rate constant of TCA in women than in men in his human physiologically based pharmacokinetic models for TCE. An experimental study using guinea pigs also showed a sex difference in TCE metabolism²²). When the sex was included in the final equation in the present study, mean and 95% PI of end-of-shift TCA concentrations in male and female patients were estimated to be 64 and 5.4–760, and 107 and 13–850 mg/l, respectively. Whether or not there is a sex difference in the disease susceptibility should be investigated in future studies along with possible difference in the TCE exposure and the metabolism between sexes. Another consideration is whether the BHLs of urinary TCE metabolites vary among individuals with different genetic backgrounds. Notably, individual susceptibility differs greatly among exposed workers, and *HLA-B** polymorphism is a particular risk factor; approximately 70% of Chinese patients²³) and one Japanese patient⁸) with TCE HS carry the *HLA-B*13:01* polymorphism, and carriers of this polymorphism are more susceptible to TCE HS²³). Of 78 patients included in the present study, we applied HLA-B genotyping to 32 patients. Twenty (62.5%) of the 32 had *HLA-B*13:01* (manuscript in preparation). Currently, no information is available regarding whether the aforementioned factors can affect the BHL of urinary TCA, and this should be explored in future studies.

Our goal is the prevention of TCE HS in the workplace. In the literature, environmental or personal exposure concentrations of TCE were likely higher than 135 mg/m³ (50 ppm), an Occupational Exposure Limit set by the Japan Society for Occupational Health, in many of the HS cases, while there was a case whose TWA exposure concentration should have been lower²). The present study results were consistent with those in the literature, and also showed that the estimated mean concentration (83 mg/l)

and 95% PI (9.6–720 mg/l) in the end-of-shift urine overlapped with that of the exposed workers without HS from six factories where HS occurred (geometric mean, 127 mg/l; 95% CI 16–984 mg/l). Though it might appear that the concentration range in the HS patients was lower than that in the exposed workers without HS, this is an issue to be investigated in future studies. However, an important finding should be stressed that HS occurred in the environment where the workers were exposed to the TCE concentration corresponding to the urinary TCA concentration as low as 10 mg/l. Thus, controlling the exposure individually with reference to urinary TCA concentrations is a warranted strategy: exposure to TCE should be restricted to levels at which urinary TCA concentrations remain <10 mg/l as preliminary reference values. Although genetic factors such as *HLA-B*13:01* are important predispositions to TCE HS, it is essential to reduce the exposure to the level at which an occurrence of the disease, which can be fatal, should be prevented regardless of the genetic factors.

Finally, the following important limitations should be considered when interpreting the present results. First, as mentioned, TCE metabolism might differ between HS patients and healthy workers. Second, it may be controversial to compare the estimated urinary TCA levels in HS patients with the OEL-B in Japan or the BEI in ACGIH^{10, 14} because such guideline values should be compared with data derived from urine specimens collected at specific times (i.e., within 2 h before the end of a shift at the end of a workweek). However, we believe that the statistical approach used in the present study is the best possible one to estimate the TCA levels in the end-of-shift urine when the intervals between the last exposure and urine sampling cannot be controlled.

In conclusion, although there is an inevitable uncertainty in the estimation process, it was suggested that TCE HS occurred in the environment where the workers were exposed to the TCE concentration corresponding to the urinary TCA concentration as low as 10 mg/l. Further studies are needed to clarify if this level is relevant to protect the workers from the disease.

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Conflicts of interest

None.

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