

# Trichloroethylene in Urine as Biological Exposure Index

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**Abstract:** Occupational exposure to trichloroethylene (TRI) was studied by analysis of environmental air and urine from 49 workers operating in a special printing house on glass. For the measurement of environmental concentration of TRI ( $C_{env}$ ), the ambient air was sampled using personal passive dosimeters. The activated charcoal was desorbed with carbon disulfide and injected into a gas-chromatograph – mass spectrometer (GC-MSD). The biological monitoring of exposed workers was conducted by determining the concentration of TRI in urine ( $C_{urine}$ ). Urine concentration of TRI was determined by headspace analysis using GC-MSD. Significant correlation was found between the environmental TRI concentration and urinary TRI concentration. The use of a regression equation between  $C_{urine}$  ( $\mu\text{g/l}$ ) and  $C_{env}$  ( $\text{mg/m}^3$ ) ( $C_{urine} = 0.081 \times C_{env} + 4.27$ ) resulted in a value of  $C_{urine}$  corresponding to Threshold Limit Value-Time Weighted Average (TLV-TWA) exposure value ( $269 \text{ mg/m}^3$ ) of  $26.0 \mu\text{g/L}$ .

**Key words:** Trichloroethylene, Urine, Biological exposure index

## Introduction

Trichloroethylene (TRI) is a colorless liquid with a strong odor and a vapor pressure of 58 torr at room temperature, it was widely used in industries for soluble agent and cleaner. It is present in the air of the workplace as a vapor. It is poorly soluble in water (1.1 mg/ml) and very soluble in organic solvents and lipids. The tissue-gas partition coefficients at 37°C are about 9.5 for blood, about 20 for lean tissue, and about 600 for fat<sup>1</sup>. The utilization of TRI is limited for its possible carcinogenicity now, but it is still used in some industries.

In the workplace, TRI is mainly absorbed via the lungs. When the skin is contacted with liquid TRI, dermal absorption may be significant, if the workers have a good hygiene knowledge, this route of absorption is not important. At steady-state, about 60% of inhaled TRI enters blood circulation<sup>2-5</sup>, which represents an uptake rate of 3.2 mg/min during exposure to the current TLV-TWA of 269 mg/

$\text{m}^3$ . TRI can be eliminated unchanged in exhaled air and urine, a large part can be eliminated as metabolites in urine<sup>5</sup>. A small part (about 8%) of the metabolites are excreted in feces and sweat<sup>2</sup>. Following an 8-hour exposure, volunteers exhaled about 9% of the pulmonary uptake. The elimination seemed to be in three phase, with elimination half-lives of 20 minutes, 3 hours, and 30 hours<sup>3</sup>. The urinary excretion of metabolites is slower than pulmonary elimination of original type of TRI. The apparent elimination half-lives are 50 to 100 hours for trichloroacetic acid (TCAA)<sup>2, 6-7</sup> and about 12 to 26 hours for trichloroethanol (TCOH)<sup>2, 6-8</sup>. TRI is metabolized by a mixed-function oxidase system to the short-lived epoxide, which facilitates the migration of chloral hydrate, latter is rapidly oxidized to TCAA or reduced to TCOH, which is conjugated to glucuronide or oxidized to TCAA. A significant binding of TRI to mitochondrial and endoplasmic proteins and lipids is associated with carcinogenic and mutagenic potential of high level of TRI exposure. The relationship between the degree of exposure and TCOH excretion, total trichloro-compounds(TTC), the sum of TCAA, and free and conjugated TCOH expressed

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as TCAA remain linear below  $1600 \text{ mg/m}^3$ <sup>3,9</sup>). Measurement of TCAA and TCOH in urine and blood are recommended for biological monitoring of exposure to TRI. But both determinants are non-specific indicators of exposure to TRI because they can be metabolites of other chlorin-containing ethanes and ethylenes<sup>10</sup>. Monitoring of TRI in exhaled air or blood is recommended as confirmatory test whenever there is a doubt about the origin of TCAA or TCOH. TCAA in urine is regarded as the best indicator of integrated exposure over the workweek<sup>10</sup>. Free TCOH in blood is a measure of recent exposure (exposure during the workshift). Concentrations of both metabolites in urine are indicators of both integrated and recent exposures. Their concentrations in samples collected at the end of the shift and at the end of the workweek are almost equally affected by exposure during the last shift and by exposures over the workweek. The measurements of TCAA in urine have been made<sup>11–14</sup>, and also the measurements of TRI and TCOH in blood<sup>13–16, 9</sup>). But the measurement of TRI in urine has not been reported until now. In general, measuring the original solvent in urine is easier than which in blood, and more practical. We performed a study on relationship between urine TRI concentration ( $C_{\text{urine}}$ ) and air TRI concentration ( $C_{\text{env}}$ ) collected at breathing zone of workers in workplace, in order to get regression equation, then to go back to the urinary concentration corresponding to the Threshold Limit Value-Time Weighted Average (TLV-TWA) level of exposure, and to propose BEI for TRI in urine. The TCAA concentration in urine is studied too.

## Materials and Methods

The survey was performed two times in a year, on the entire 49 workers (8 male, 41 female) with a mean age of 38 years (range =21–59) employed in a special printing house which prints on glass and exposed to TRI levels generally lower than  $296 \text{ mg/m}^3$ . The physical demands of the job were practically the same for all subjects and functions. One working shift (8 h daily) was considered from 8 AM to 5 PM, with a hour meal break period at 12. TRI environmental concentration in the breathing zone was measured during the first exposure period of 4 h by means of personal passive samplers. Urine samples ( $C_{\text{urine}}$ ,  $\mu\text{g/l}$ ) were collected from workers at 12. None of the subjects experienced workplace exposure to TRI during the sixteen hours prior to the onset measurement.

The time weighted average (TWA) of the concentration of TRI to which each subject was exposed ( $C_{\text{env}}$ ,  $\text{mg/m}^3$ ) was measured with personal passive samplers (TK-200

Zambelli, Italy). TRI present in the activated charcoal was desorbed with carbon disulfide, and the extract was injected into a gas chromatograph — mass spectrometer (GC-MSD). The coefficient of variation of the method was 8.5%.

Urine samples were removed at the beginning of the exposure (8 AM) and collected after four hours, at noon. Sampling was performed in a non polluted environment where the TRI concentration in the ambient air was  $< 100 \mu\text{g/m}^3$ . Sample containers were immediately tightly capped as soon as collection was over. In this way, exposure of the sample to air was very low with negligible loss of solvent. After collection, a headspace air sample of 0.5 ml was subsequently analyzed by a GC-MSD. The analytical conditions for the gas chromatograph were as follows: cross-linked column 5% phenyl methyl silicone (internal diameter 0.2 mm, length 25 m) column temperature:  $100^\circ\text{C}$ ; carrier gas: helium; retention time of TRI: 2.26 minutes. The analytical conditions for the mass selective detector were: monitored ion: 130; dwell time: 100 ms; selected ion monitoring window time: 0.1 amount unit; electromultiplier voltage: 2000 V.

An aqueous standard solution of TRI was prepared by dissolving 1 ml (1,4649 g) of TRI in 100 ml of acetone and diluting 1 ml of this solution in 1 L of water; the resulting solution ( $14650 \mu\text{g/l}$ ) was diluted in steps to prepare five additional aqueous standards whose concentration ranged down to  $3 \mu\text{g/l}$ . The reliability of the dilution procedure was checked by analysis of the various aqueous standards. Five duplicate standard samples of urine were prepared from pooled urine from ten donors, by substituting 1 ml of the appropriate aqueous standard for pure water in the sample collection procedure, together with five blanks from the same urine. The calibration plot showed an excellent linearity up to at least  $732 \mu\text{g/l}$  of TRI. Recovery tests were conducted by adding known amounts of TRI to urine having a very low content of solvent ( $< 0.1 \mu\text{g/l}$ ); each test involved two additions (concentration range  $5\text{--}60 \mu\text{g/l}$ ). These experiments ( $n=5$ ) gave recovery values of 97.9–102.5%. The TRI Limit of Quantitation (LOQ) in biological and environmental samples with this method was  $0.10 \mu\text{g/l}$  and  $0.10 \text{ mg/m}^3$ , respectively. The coefficient of variation (CV) for urine ( $\text{CV}=\text{Standard Deviation}/\text{Mean Value}$ ) of the method was 7.9% on 10 determinations, with mean values of  $15 \mu\text{g/l}$ . Although no significant loss of TRI from urine was noted in samples that have been stored for 10 days, all urinary determinations were carried out within 5 days of specimen collection.

TCAA was determined by a GC-MSD method published previously<sup>17</sup>). Creatinine concentration in urine was measured

**Table 1. Results of the environmental and biological monitoring (AM, arithmetic mean, ASD arithmetic standard deviation, GM geometric mean, GSD geometric standard deviation)**

Variable	No. of subjects	range	AM	+/- ASD	GM	GSD
Airborne trichloroethylene levels (mg/m <sup>3</sup> )	49	2.7–387.0	83.31	86.36	44.05	3.37
Urinary trichloroethylene (µg/l)	49	0.8– 43.9	11.03	8.29	7.99	2.46
Urinary trichloroacetic acid (mg/g. creat.)	49	0.4– 57.3	21.60	18.25	10.86	4.48

by the method of Jaffe.

All statistical analyses were performed with StatView software. A simple linear regression was performed with environmental TRI as the independent variable and urinary TRI as dependent variable. A test was considered statistically significant with value of  $p < 0.05$ . Regression analyses between urine and environmental concentrations were conducted to establish exposure-excretion relationships.

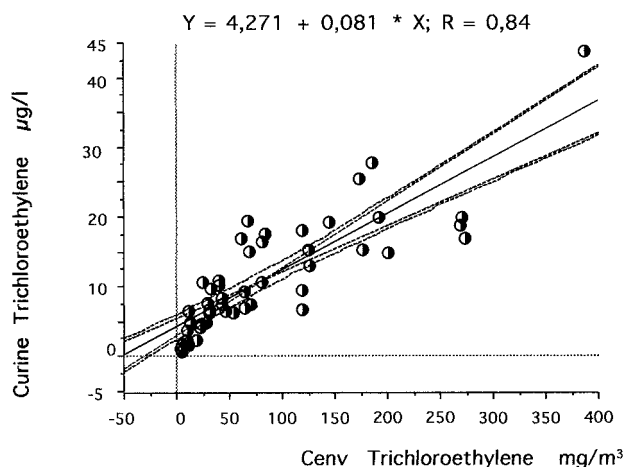
## Result

The mean value for exposure of TRI in breathing zone of workers was 83.31 mg/m<sup>3</sup>, (SD = ± 86.36), which is below the 2000 ACGIH TLV(TWA)<sup>18)</sup> (269 mg/m<sup>3</sup>), whereas TRI in urine ( $C_{urine}$ ) was 11.0 mg/L (SD = ± 8.29). The mean concentration of TCAA in urine was 21.6 mg/L (SD = ± 18.25). In Table 1 we summarized all results. In order to search the relationship between TRI in the air of workplace ( $C_{env}$ ) and that in urine ( $C_{urine}$ ), a regression analysis was performed. The result is shown in Fig. 1. Two groups of data were regressed well,  $C_{urine} = 4.271 + 0.081X C_{env}$ ;  $r = 0.84$ ;  $p < 0.0001$ .

The urine TCAA mean value is lower than the ACGIH BEI (100 mg/g creatinine), and also lower than the no-effect levels suggested by different authors: 50 mg/L by Frant and Westendorp<sup>19)</sup>; 75 mg/L by Suchanova and Burdigina<sup>20)</sup>; 100 mg/L by Teisiger *et al.*<sup>21)</sup> and Bardodej<sup>22)</sup>, almost equal, only a little higher than 20 mg/L supposed by Ahlmark and Firssman<sup>23)</sup>. Contradictory to the regression result between TRI ( $C_{env}$ ) and TRI ( $C_{urine}$ ), the regression between TRI ( $C_{env}$ ) and TCAA in urine is poverty,  $TCAA = 17.03 + 0.059x (C_{env})$ ;  $r = 0.32$ ;  $p = 0.051$  and this because the samplers of urine were collected in the first days of the week.

## Discussion

Trichloroethylene (TRI) has been widely used as a solvent and a cleaner, and has become a major groundwater contaminant. TRI is a well-recognized animal carcinogen. Though its risk for carcinogenicity to human is still not



**Fig. 1. Scatter diagram relating the time-weighted average of environmental concentration (in the breathing zone) ( $C_{env}$ ) and the urinary concentration ( $C_{urine}$ ) of Trichloroethylene. The curves indicating upper and lower confidence limits of 95% are given and the regression line is also drawn.**

exactly recognized, some epidemiological studies have linked it with increased incidence of urinary-tract tumors and lymphomas in TRI exposed workers and with childhood leukemia. Consequently, the accuracy and appropriateness of regulatory limits on TRI exposure have been uncertain. For example, the American Conference of Governmental Industrial Hygienists (ACGIH) classified TRI as a Group A5 carcinogen, “Not suspected as a human carcinogen”, in 1992, with a recommended TLV-TWA of 269 mg/m<sup>3</sup><sup>24)</sup>. The International Agency for Research on Cancer (IARC) had previously classified it as a Group 3 chemical: “not classifiable as to carcinogenicity to humans”<sup>25)</sup>. However, IARC reevaluated TRI in 1995 and reclassified it as a Group 2A carcinogen, “probably carcinogenic to humans”<sup>26)</sup>. So its environmental measurement in workplace and biomonitoring for exposed workers play a very important role.

The environmental TRI concentration ( $C_{env}$ ) is the determinant of the TRI concentration in blood and in urine ( $C_{urine}$ ), and the concentration of its metabolites both in blood and urine. We know the blood and urine TRI concentrations

and the concentrations of its metabolites are “exposure biomarkers”. The exposure biomarker should reflect “real environmental exposure” well. The environmental measure of chemicals is not exactly the “real exposure” of exposed workers, because it does not reflect the inhaled dose, though the sample is collected in the breathing zone of exposed workers. From this point of view, good biomarkers are more important for evaluating the “exposed dose” of chemicals and the risk to human health. For a TLV-TWA of 269 mg/m<sup>3</sup> the ACGIH recommends the following biological exposure indices (ACGIH, 2000)<sup>18</sup>:

- (a) Trichloroacetic acid in urine -end of workweek 100 mg/g creatinine
- (b) Trichloroacetic acid and trichloroethanol in urine- end of shift at end of workweek 300 mg/g creatinine
- (c) Free trichloroethanol in blood - end of shift at end of workweek 4 mg/l
- (d) Trichloroethylene in blood
- (f) Trichloroethylene in end-exhaled air

Measurements of TCAA and TCOH in urine and blood are recommended for biological monitoring of exposure to TRI, but both determinants are thought non-specific indicators of exposure to TRI, because they can be metabolites of other chlorine-containing ethanes and ethylenes. Monitoring of TRI in exhaled air or blood is recommended as a confirmatory test whenever there is a doubt about the origin of TCAA or TCOH. It is said that TCAA in urine is the best indicator of integrated exposure for all the workweek. Free TCOH in blood reflects the recent exposure (exposure during the workday). Values measured in urine for both metabolites are indicators of both integrated and recent exposures. Their concentrations in samples collected at the end of the workday at the end of the workweek are thought to be almost equally affected by exposure during the last workday and by exposure during all the workweek. Some investigators suggest that the correlation between the TRI concentration in environmental air and TCAA excretion in urine is linear only if the exposure concentration is below 269 mg/m<sup>3</sup><sup>9, 27–29</sup>. Some other investigators did not observe the nonlinearity. Because of the large interindividual variation and protein binding to TCAA<sup>6</sup>, some investigators consider the determination of TCAA in urine as a very poor measure of TRI exposure<sup>30</sup>. Our result seems to concord with the opinion described above even if the urine samples were collected in the first day of the week.

In order to avoid overestimation of exposure to TRI, it is important to offer multiple choices of tests which can be used for the assessment of uptake in the workroom environment. A direct determination of TRI in urine by GC

has been used, but the validity of the test was studied only for qualitative purposes. The aim of the present research was to determine the Biological Index of TRI. Therefore, we quantified the relation between  $C_{env}$  and  $C_{urine}$ . We found a strong linear relationship between TRI in urine and environmental TRI exposure ( $r=0.84$ ,  $p<0.0001$ ). Since the distribution of both the environmental and biological values was fairly skewed, a logarithmic transformation of the variables was performed. A slight increase in correlation coefficient was observed ( $r=0.90$ ),

For an exposure to 269 mg/m<sup>3</sup>, the corresponding calculated concentration for urinary TRI is 26.0  $\mu\text{g/l}$  and its 95% lower confidence limit is 20.2  $\mu\text{g/l}$  (lower straight-line of experimental straight line:  $C_{urine}=0.055 C_{env} + 3.041$ ). This value can be considered as the biological equivalent exposure limit (BEEL) for TRI in urine. The regression line did not start from the origin of the Cartesian coordinates, but it intercepted the y axis at + 4.2  $\mu\text{g/l}$ ; this finding indicated that at the beginning of the exposure period there was a low concentration of TRI in the urine of subjects under study. The presence of TRI in the pre-shift urine of persons exposed possibly can be explained by a temporary storage of TRI in the adipose tissue.

The measurement of TRI in urine by means of GC/MSD is not complicated and easy to perform. The TRI in urine is detectable with our method, and the values are correlated well with the environmental concentrations. So the concentration of TRI in urine should be a sensitive and practical biomarker of TRI exposure. We suggest that it could be utilized as a conventional practice of measurement for TRI exposure.

The concentrations of TRI in air, venous blood, urine and TRI metabolites are different as regards their meaning. The respiratory compartment communicates directly with the environment. Therefore it follows its variations very rapidly. For this reason, single alveolar samples collected during exposure reflect the instantaneous environmental values immediately preceding sampling. Thus, in order to obtain an alveolar value which can represent a mean exposure value, numerous alveolar samples must be taken during exposure (multiple instantaneous samples). The blood level of TRI is similar in some ways to the alveolar compartment. The urine is the site of excretion of TRI absorbed via the inhalation route. The urinary concentration values of metabolites and TRI eliminated unchanged (non-metabolized portion) are always “weighted” values, since the bladder acts as a collecting and mixing vessel for urine formed in the kidney. However, the exposure time represented by the metabolites is different from the time represented by TRI in urine. TRI

is poorly soluble and equilibration among environmental air, alveolar air, and arterial and renal venous blood takes place very rapidly, within a few minutes. This means that the fluctuations in environmental concentrations are rapidly reflected at the urinary level because the urine, newly formed in the kidney, can be considered as a liquid sample in equilibrium with renal blood. Assuming a sufficient constant production of urine over time, the concentration value of the TRI in urine, formed during and collected at the end of exposure, corresponds to the weighted average value of a sample of air breathed during the time urine collects in the bladder (exposure time). This study shows that the relationship between  $C_{\text{urine}}$  and  $C_{\text{env}}$  does not improve when the values of TRI in urine are corrected for urinary creatinine or for specific gravity; this confirms what has been seen with other solvents<sup>31)</sup>.

The TRI in urine value can be regarded as a TWA, reflecting exposure during the 4-h period. The TRI urinary weighted values, measured in samples of urine produced throughout the exposure and collected at the end of it, provide an appropriate index of the magnitude of exposure during the production time of urine. The urinary TRI concentrations should be proportional to those in the arterial blood, with a proportional coefficient corresponding to the  $\lambda$  blood/urine value, on the assumption that the exchange of the solvent between the arterial blood and urine occurs after simple partition in accordance with Henry's law. In the case of TRI and in most solvents used in industry<sup>32)</sup>, once a constant arterial concentration value has been reached in 2 hours exposure, the slope of the regression line (TRI in urine — TRI in breathing zone air) should be independent of exposure time. After the 2 hours exposure the biological half-life of solvents does not need to be taken into consideration. The collection of urine after 4 hours exposure guarantees that the pressure balance among TRI in air, TRI in arterial blood and TRI in urine has been reached.

As a conclusion, the biological monitoring of occupational exposure to TRI is feasible by adopting various strategies and methods. A satisfactory level of sensitivity and specificity can be achieved at the low level of exposure usually encountered today in the industrial environment. We believe that the concentration in urine can be an appropriate indicator of exposure to TRI.

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