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Rapid Determination of Volatile Organic Compounds in Human Whole Blood Using Static Headspace Sampling with Gas Chromatography and Mass Spectrometry

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Headspace (HS) and headspace solid-phase microextraction (HS-SPME) were studied for extracting volatile organic compounds (VOCs) from whole blood, with chemical and instrumental variables being optimized for maximum sensitivity: incubation at 60 °C, equilibration for 30 min, pH 11, and 2 mL injection volume. Both techniques provided accurate analyses, with detection limits of 0.05-0.1 ng mL^{-1} and 0.05-0.5 ng mL^{-1}. HS showed better sensitivity, reproducibility, and analysis times than HS-SPME. Overall levels of chloroform in whole blood were found to be 0.05-5.84 ng mL^{-1}; detected levels of benzene were 0.05-2.20 ng mL^{-1}.

Key Words : VOCs, Whole blood, Headspace, HS-GC-MS

Introduction

Industrially released volatile organic compounds (VOCs) can threaten human health.[1]

Harmful examples include chloroform, benzene, toluene, ethylbenzene and xylenes. Chloroform can cause persistent liver toxicity.[2,3] Benzene, an important petrochemical product and paint solvent, can decrease the number of red blood cells, leading to anemia and DNA breakage.[4,5] Toluene can be metabolized to toxic compounds; 5% of its metabolites are oxidized to benzaldehyde and cresols.[6,7] Most of the reactive products are detoxified by conjugation to glutathione but the remainder may severely damage cells.[8] Ethylbenzene and xylenes, important petrochemicals, can irritate the nose and throat upon inhalation, producing symptoms of central nervous system depression and affecting the liver and kidneys.[9]

The various symptoms imputed to VOCs lead them to being considered potentially hazardous to human health.[10] Therefore, it is important that their presence in human blood be analyzed to assess effectively their effects on health.

Because VOCs have comparatively low boiling points and high vapor pressures, their determination in aqueous samples is usually carried out by gas chromatography (GC) with mass spectrometry (MS) using one of three sampling techniques: purge & trap, headspace solid-phase microextraction (HS-SPME), and static headspace (HS).

Purge & trap sampling involves sparging samples with helium for a few minutes so as to remove any VOCs to a cool adsorbent trap. A carrier gas then flows through the trap, which is heated for a few minutes to desorb the VOCs to GC apparatus.[11]

In HS-SPME, VOCs are adsorbed directly from the sample onto polymer-coated fused-silica fiber. The fiber is then removed and the VOCs are thermally desorbed and injected into a gas chromatograph.[12,13] HS-SPME has been used in the determination of various pollutants, such as pesticides,[14,15] PAHs, PCBs,[16-19] and phenols.[20,21] It has also been used to measure inorganic and organometallic compounds.[22-24] However, less volatile sample compounds and solvents can remain on the column, reducing its life-time and interfering with subsequent analyses.[25]

HS involves heating samples in sealed vials until the volatile compounds reach equilibrium with the gas phase, which is then analyzed by gas chromatography.[13,26] The concentration of the analyte (C_g) in the headspace depends on its partition coefficient (K) and initial concentration (C_0), and the volume ratio ($V_r + V_g$) of the gas phase to the liquid phase at equilibrium as described by Eq. (1).[27]

$$C_g = \frac{C_0 V_s}{K(V_r + V_g)} \quad (1)$$

HS-GC is influenced by the equilibrium temperature through the temperature dependence of K.[28] Therefore it is important to optimize the temperature of equilibration to maximize analytes' extraction.

Headspace sampling can employ either static or dynamic injection systems. Dynamic HS is more sensitive than static HS, though it cannot be readily automated and is restricted to aqueous solutions.[29] Therefore the aqueous samples of this study would require static HS.

All three sampling techniques can provide highly sensitive analyses. However, purge & trap is not suitable to determine VOCs in biological fluids because it requires large sample volumes and the sparger can be contaminated by biological fluids.[30] HS-SPME and HS are suitable to analyze VOCs in biological fluids, providing highly sensitive analyses of small samples and not requiring complicated instrumentation or organic solvents.[13]

This work reports the implementation of HS-GC-MS to

determine VOCs. Matrix effects in the HS analysis were compensated for by the use of internal standards. HS sampling was compared with HS-SPME. The developed HS technique was applied to determine the levels of analytes in the whole blood of humans living near industrial sites.

Materials and methods

Standards and Chemicals. EPA 524.2 VOC mix (containing dichlorodifluoromethane, chloromethane, vinyl chloride, bromomethane, chloroethane, trichloro-fluoromethane, 1,1-dichloroethylene, methylene chloride, *trans*-1,2-dichloroethylene, 1,1-dichloroethane, 1,2,2-dichloroethane, *cis*-1,2-dichloroethylene, chloroform, bromochloromethane, 1,1,1-trichloroethane, 1,1-dichloropropene, carbon tetrachloride, 1,2-dichloroethane, benzene, trichloroethylene, 1,2-dichloropropane, bromodichloromethane, dibromomethane, cis-1,3-dichloro-propene, toluene, *trans*-1,3-dichloropropene, 1,1,2-trichloroethane, 1,3-dichloropropane, tetrachloroethylene, chlorodibromomethane, 1,2-dibromomethane, chlorobenzene, 1,1,1,2-tetrachloroethane, ethylbenzene, *m*-xylene, *p*-xylene, *o*-xylene, styrene, isopropylbenzene, bromoform, 1,1,2,2-tetra-chloroethane, 1,2,3-trichloropropane, *n*-propylbenzene, bromobenzene, 1,3,5-trichlorobenzene, 2-chlorotoluene, 4-chlorotoluene, *tert*-butylbenzene, 1,2,4-trimethylbenzene, *sec*-buthylbenzene, *p*-isopropyltoluene, 1,3-dichloro-benzene, 1,4-dichlorobenzene, *n*-butylbenzene, 1,2-dichlorobenzene, 1,2-dibromo-3-chloropropane, 1,2,4-trichlorobenzene, hexachlorobutadiene, naphthalene, and 1,2,3-trichlorobenzene at 200 ng mL^{-1} in methanol, shown Fig. 1, and fluorobenzene and 1,2-dichlorobenzene-d_4 (2000 ng mL^{-1} in methanol) were from Supelco (Bellefonte, PA, USA). 1,3-Butadiene (200 ng mL^{-1} in methanol) was from Accustandard (New Haven, CT, USA). Stock solution of 100 ng mL^{-1} in methanol was prepared to 1:1 mix of EPA 524.2 VOC mix and 1,3-butadiene solution. Sodium chloride was from Junsei (Junsei Chemical, Japan). All standard solutions were prepared with methanol (HPLC-grade) from Burdic & Jackson (Muskegon, MI, USA) and stored in glass-stoppered bottles at 4 °C in the dark. Working solutions were prepared by series diluting the stock solutions with methanol.

Instruments and Apparatus. HS was conducted with an autosampler (Combi-PAL, CTC Analytics AG, Zwingen, Switzerland) and a gas chromatograph (HP 6890, Agilent Technologies, Palo Alto, CA, USA) equipped with a mass selective detector (HP 5973N, Agilent Technologies, Palo Alto, CA, USA). Injection was in split mode (split ratio 100:1) to a fused silica capillary column (VOCOL^{TM} 60 m × 0.32 mm I.D × 1.5 μm, film thickness). Mass spectra were obtained at 70 eV in electron ionization mode. The spectrometer was operated in selected ion monitoring (SIM) mode. Full-scan mass spectra (*m/z* 35-450) were recorded only for analyte identification. The source and analyzer temperatures were 230 and 150 °C, respectively (Table 1). Total ion chromatograms were acquired and processed using G1701DA D.01.02 standalone data analysis software (Agilent Technologies) that was also used to control the whole system.

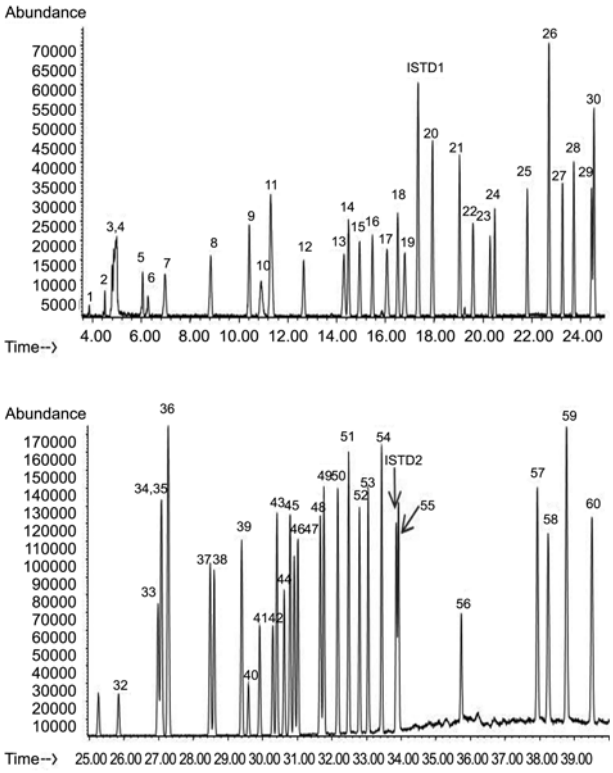

Figure 1. HS-GC/MS total ion chromatogram of VOCs standards; 1: Dichlorodifluoromethane, 2: Chloromethane, 3: Vinyl chloride, 4: 1,3-Butadiene, 5: Bromomethane, 6: Chloroethane, 7: 1,1-Dichloropropene, 8: Trichlorofluoromethane, 9: 1,1-Dichloroethylene, 10: Methylene chloride, 11: *trans*-1,2-Dichloroethylene, 12: 1,1-Dichloroethane, 13: 2,2-Dichloropropane, 14: *cis*-1,2-Dichloroethylene, 15: Chloroform 16: Bromochloromethane, 17: 1,1,1-Trichloroethane, 18: Carbon tetrachloride, 19: Benzene, ISTD1: Fluorobenzene, 20: 1,2-Dichloroetane, 21: Trichloroethylene, 22: 1,2-Dichloropropane, 23: Bromodichloromethane, 24: Dibromomethane, 25: 1,1,2,2-Tetrachloroethane, 26: *cis*-1,3-Dichloropropene, 27: Toluene, 28: *trans*-1,3-Dichloropropene, 29: 1,1,2-Trichloroethane, 30: 1,3-Dichloropropane, 31: Tetrachloroethylene, 32: Dibromochloromethane, 33: 1,2-Dibromoethane, 34: Chlorobenzene, 35: Ethylbenzene, 36: 1,1,1,2-Tetrachloroethane, 37: *m*-/*p*-Xylene, 38: *o*-Xylene, 39: Stylene, 40: Isopropylbenzene, 41: Bromoform, 42: 1,2,3-Trichloropropane, 43: *n*-Propylbenzene, 44: Bromobenzene, 45: 1,3,5-Trimetylbenzene, 46: 2-Chlorotoluene, 47: 4-Chlorotoluene, 48: *tert*-Butylbenzene, 49: 1,2,4-Trimethylbenzene, 50: *sec*-Butylbenzene, 51: *p*-Isopropyltoluene, 52: 1,3-Dichlorobenzene, 53: 1,4-Dichlorobenzene, 54: *n*-Butylbenzene, ISTD2: 1,2-Dichlorobenzene-d_4, 55: 1,2-Dichlorobenzene, 56: 1,2-Dibromo-3-chloropropane, 57: 1,2,4-Trichlorobenzene, 58: Hexachlorobutadiene, 59: Naphthalene, 60: 1,2,3-Trichlorobenzene.

HS-SPME. The SPME device and fiber were from Supelco (Bellefonte, PA, USA). The 10 mm long microextraction fiber was coated with 85 μm thick CAR/PDMS (polydimethylsiloxane) film. New fiber was conditioned for 1-2 h in a GC injector port at 300 °C before being used in analysis. The conditioned fiber was used immediately or protected from contamination by inserting the SPME syringe needle into a GC septum injection port before use.

HS-SPME sampling was optimized with sampling for 2 min; stirring at 500 rpm; desorption at 250 °C for 0.5 min; with 2 mL sample volumes (1 mL whole blood and 1 mL

Table 1. GC/MS instrumental conditions for the analysis of VOCs

GC				
Column	VOCOL (60 m × 0.32 mm I.D. × 1.5 um film thickness)			
Carrier gas	He at 1.5 mL/min (EPC: constant flow)			
Split ratio	split (100:1)			
Injection port temp.	200 °C (250 °C in HS-SPME condition)			
Oven equilibrium time	3.0 min			
Oven temp. program				
Initial temp. (°C)	Initial time (min)	Rate (°C/min)	Final temp. (°C)	Final time (min)
35	5	3	50	0
		5	130	0
		8	200	6
Run Time 40.75 min				
MS				
Transfer line temp.	200 °C			
Ionization mode	Electron impact (EI)			
Electron energy	70 eV			
Ion source temp.	230 °C			
Analyzer	Quadruple (temp. 150 °C)			
Detection mode	SIM mode			
Scanning range	*m/z* 35-450			

Table 2. Optical parameters of HS-SPME method for the extraction of VOCs in whole blood

Parameter	Whole blood
Volume	2 mL (blood 1 mL/water 1 mL)
Salt (NaCl)	0.4 g
pH control	K_2CO_3 0.04 g
Adsorption temp. (°C)	30 °C
Adsorption time (min)	50 min
Desorption temp. (°C)	250 °C
Desorption time (min)	0.5 min
Agitator speed	500 rpm

water) in 11 mL vials. 2 mL samples were placed in 4 mL glass vials with silicon-septum caps, spiked with VOCs, and mixed with 0.4 g sodium chloride and 0.04 g potassium carbonate anhydride to adjust to pH 11 (Table 2).

HS. Whole blood samples in 11 mL glass vials with silicon-septum caps were spiked with VOCs, and mixed with sodium chloride and HCl, citric acid, K_2CO_3 or KOH for pH control. The vials were capped and placed in the autosampler.

HS was conducted with vial equilibration for 30 min at 60 °C, 2 s stroke times for injection volume at 90 °C. Samples were agitated in sealed vials for 20, 30, 40, 50 and 60 min at 30-70 °C to determination the optimum conditions. When the VOCs reached equilibrium, the needle pierced the sealed sample vial, and the heated gas-tight syringe pumped the headspace two times. The syringe was removed from the vial and was immediately inserted into the GC injection port at 200 °C. It was then returned to its original location and cleaned with the flush gas (Table 3).

Table 3. Optical parameters of HS method for the extraction of VOCs in whole blood

Parameter	Whole blood
Volume	3 mL (blood 1 mL/water 2 mL)
Salt (NaCl)	0.6 g
pH control	K_2CO_3 0.04 g
Incubation temp	60 °C
Incubation time	30 min
Syringe temp	90 °C
Agitator speed	500 rpm
Fill speed	200 uL/s
Fill stroke	2
Pull-up delay	500 ms
Injection speed	500 uL/s
Pre inject delay	500 ms
Post inject delay	500 ms
Flush time	2 min

Results and Discussion

Optimization of HS.

Chemical Parameters:

Influence of Ionic Strength – The effects of salt added to the blood samples were first investigated. Added salt can change the blood's components' physiochemical properties including vapor and partial pressure, solubility, thermal conductivity, density, and surface tension, which would affect the vapor/liquid equilibrium. NaCl was added at 0 to 1.2 g (saturation) to spiked blank whole. Therefore, a complementary study was carried out to establish any possible loss of analytes by partial sorption on undissolved salt.

Some compounds were slightly better extracted with 0.6 g added NaCl, while the rest were either unaffected or unfavorably affected. This was possibly due to saturated blood samples hindering the extraction of VOCs from the liquid through the partial sorption of the analytes on the salt. Therefore, 0.6 g NaCl was added to the blood samples in subsequent experiments (Fig. 2).

Influence of pH – Matrix effects were minimized by regulating the pH. Extraction was tested at pH 4, 7 and 11. Otherwise neutral blood samples were acidified by citric acid or made basic with K_3PO_4. Some compounds were extracted in slightly greater amounts at pH 11, while the rest were either unaffected or unfavorably affected (Fig. 3). Therefore, subsequent experiments were conducted at pH 11.

Instrumental Parameters:

Influence of Incubation Temperature – Several instrumental parameters can affect the sensitivity and reproducibility static headspace analysis, such as oven temperature and vial equilibration time. Each autosampler also has its own unique set of parameters that result from its specific configuration. The Combi-PAL HS autosampler used here employed a gas tight syringe HS sampling device, extractions for 30 min were tested at 30-70 °C. Extraction efficiency either increased as temperature increased from 30 to 60 °C and decreased at 70 °C or was not greatly affected. The first

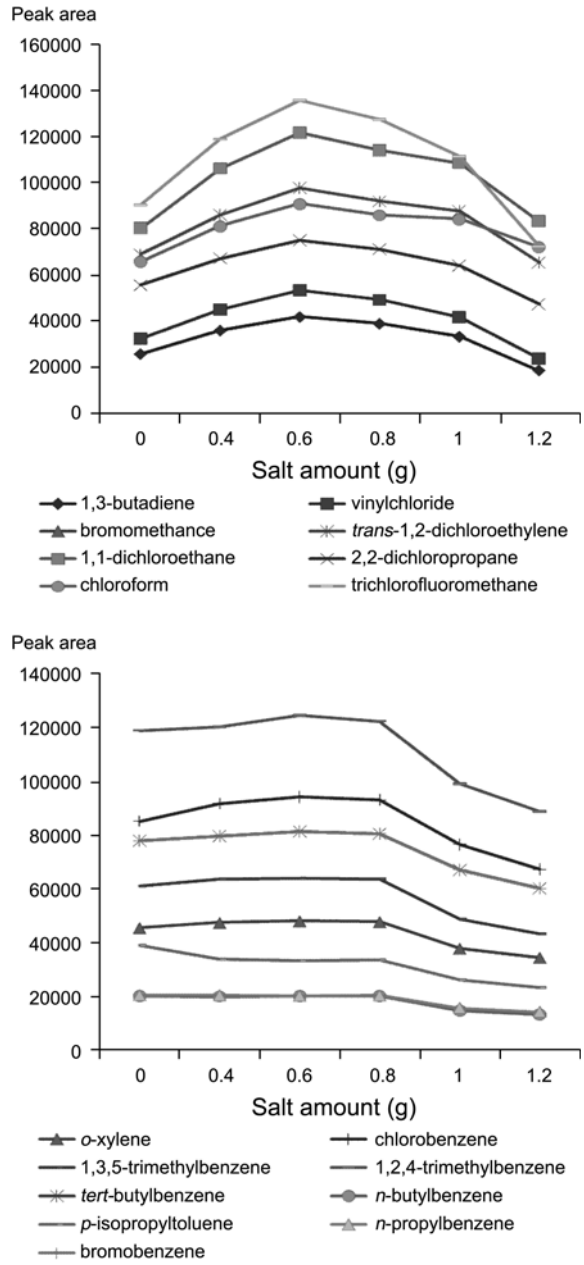

Figure 2. Salting out effects on the determination of VOCs in whole blood using HS method.

extraction pattern resulted from the solidification of the blood that hindered the volatilization of VOCs from the samples. The second type was due to the VOCs' molecular weights (MW). Some compounds with higher molecular weight were not easily volatilized and were greatly affected by the increasing temperature. Given that the efficiency of the extraction of some compounds from blood increased at higher temperatures (Fig. 4), blood samples were incubated at 60 °C in subsequent experiments.

Influence of Incubation Time – Incubation time influences the sensitivity and reproducibility of extraction. The incubation time for VOCs (Fig. 5) shows that the analytes reached equilibrium between the liquid and gas phases at 60 °C within 30 min. Therefore, subsequent HS experiments were

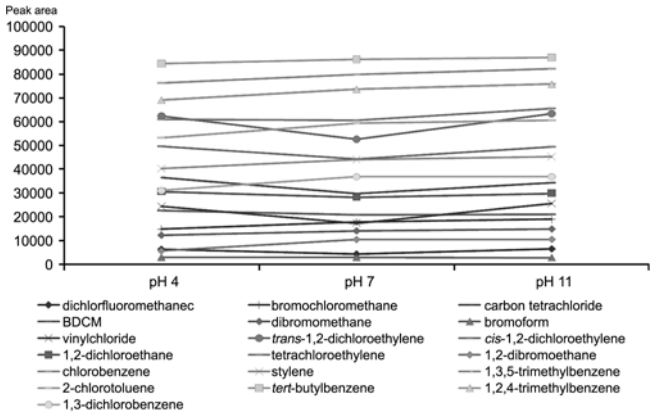

Figure 3. Effects of pH on the determination of VOCs in whole blood using HS method.

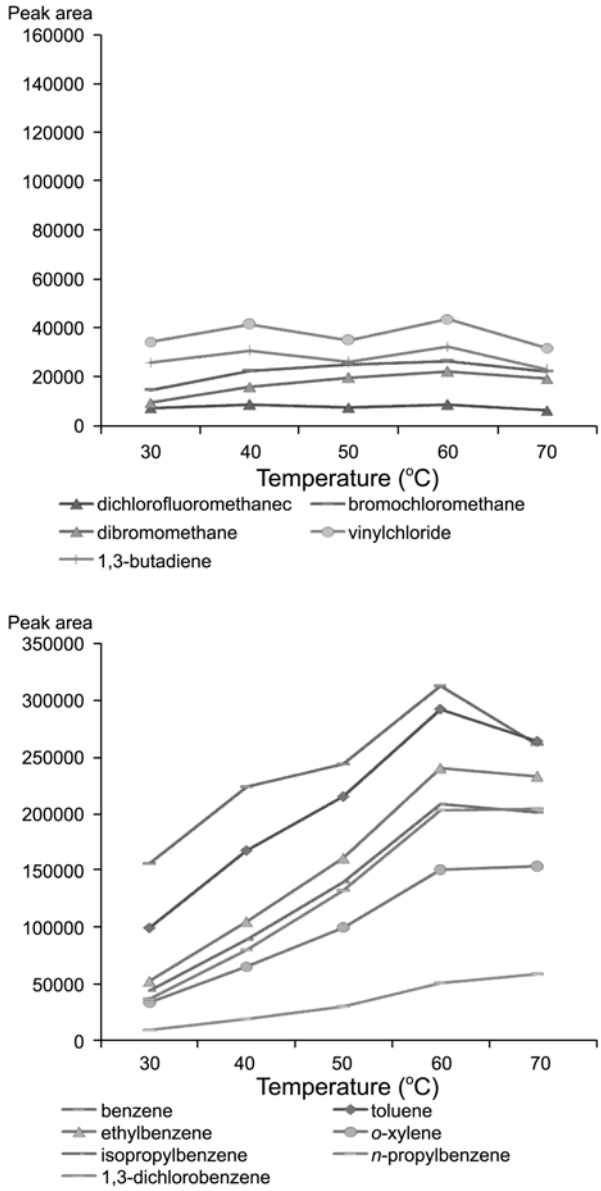

Figure 4. Effects of the incubation temperature on the determination of VOCs in whole blood using HS method.

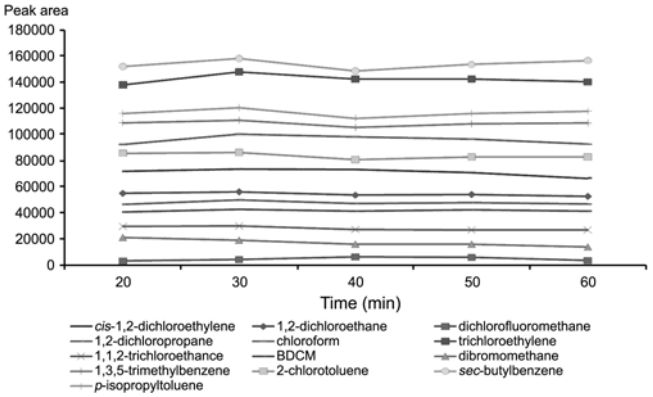

Figure 5. Effects of the incubation time on the determination of VOCs in whole blood using HS method.

incubated for 30 min.

Validation of HS Method. The performance and reliability of the proposed method were assessed by determining regression equations, sensitivities (defined as the slopes of the calibration graphs), method detection of limits (MDLs), linear ranges, precisions and accuracies for the compounds assayed. The calibration curves, MDLs, precisions and accuracies of the headspace method were measured under the optimized HS conditions (Table 3). Fluorobenzene and 1,2-dichlorobenzene-d_4 (Internal standards) were also added at 10 μg mL^{-1} to check that there were no problems with the needle of the autosampler, the carrier flow, or the split injection of the different compounds. Calibration curves for each VOC at concentrations of 0.05 to 20 ng mL^{-1} in blood were constructed by plotting the analyte-to-internal standard peak area ratio against the analyte concentration. Results for specific target VOCs are listed in Table 4.

The method's precision and accuracy for assessing blood are listed in Table 5. The relative standard deviations (RSDs) ranged from 1.35 to 8.27% and accuracies ranged from −6.78 to 14.06%.

Comparison of HS-SPME and HS. For determining VOCs in blood, HS showed lower detection limits. It could achieve results more quickly than HS-SPME, which required 50 min compared with the 30 or 20 min for HS. The relative standard deviations (RSDs) obtained by measuring five samples containing 1 ng mL^{-1} each VOC, expressed as intraday precisions, were lower for HS than for HS-SPME (Table 6).

Analysis of Real Samples. VOCs in human blood samples collected from inhabitants of industrial and control areas in

Table 5. Inter day precision and accuracy of VOCs in whole blood (n = 5)

Compound	1 ng mL^{-1}	
	Precision CV (%)[a]	Accuracy bias (%)[b]
Vinyl chloride	8.27	14.06
1,3-Butadiene	6.88	5.11
Chloroform	1.35	8.58
Benzene	2.88	-0.39
Trichloroethylene	2.97	3.90
Toluene	1.98	-2.14
Tetrachloroethylene	3.55	-0.21
Ethylbenzene	2.87	2.34
m-/*p*-Xylene	3.10	-6.78
o-Xylene	2.43	0.67

[a]: $CV\ (\%) = \frac{SD}{mean} \times 100$ SD: Standard deviation

[b]: $bias\ (\%) = \frac{outcome - true}{mean} \times 100$

Table 6. Comparision of MDL and RSD using HS-SPME and HS in whole blood (n = 5)

Compound	MDL (ng mL^{-1})		RSD (%)	
	HS-SPME	HS	HS-SPME	HS
Vinyl chloride	0.5	0.1	22.56	8.27
1,3-Butadiene	0.1	0.1	8.99	6.88
Chloroform	0.1	0.05	2.80	1.35
Benzene	0.05	0.05	4.85	2.97
Trichloroethylene	0.05	0.05	7.62	2.88
Toluene	0.1	0.05	13.04	1.98
Tetrachloroethylene	0.1	0.05	8.93	3.55
Ethylbenzene	0.1	0.05	13.46	2.87
m-/*p*-xylene	0.1	0.1	14.03	3.11
o-Xylene	0.1	0.05	13.04	2.43

Table 4. Calibration curves, linear correlation coefficient (R^2), and method detection of limit (MDL) for VOCs in whole blood

Compound	Conc. range (ng mL^{-1})	Correlation[a]	R^2	MDL (ng mL^{-1})
Vinyl chloride	0.1-20	y = 2.7491x + 0.0454	0.99	0.1
1,3-Butadiene	0.1-20	y = 0.9113x + 0.112	0.99	0.1
Chloroform	0.05-20	y = 0.6722x + 0.2142	0.99	0.05
Benzene	0.05-20	y = 1.3102x + 0.0612	0.99	0.05
Trichloroethylene	0.05-20	y = 0.5886x – 0.0113	0.99	0.05
Toluene	0.05-20	y = 1.2994x + 0.3266	0.99	0.05
Tetrachloroethylene	0.05-20	y = 0.3189x + 0.0147	0.99	0.05
Ethylbenzene	0.05-20	y = 1.1967x + 0.0267	0.99	0.05
m-/*p*-Xylene	0.05-20	y = 0.8607x + 0.0351	0.99	0.1
o-Xylene	0.05-20	y = 0.8775x + 0.0633	0.99	0.05

[a]y = analyte area-to-internal standard area, x = analyte concentration-to-internal standard concentration

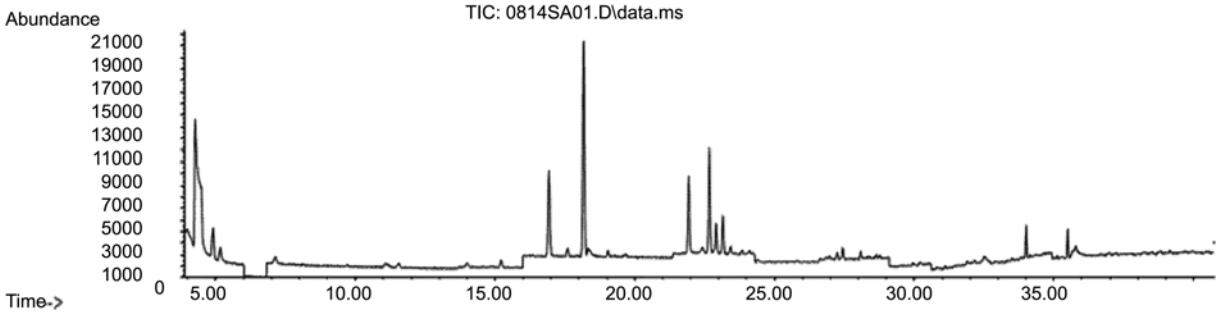

Figure 6. Total ion chromatogram of the typical sample determined using HS method.

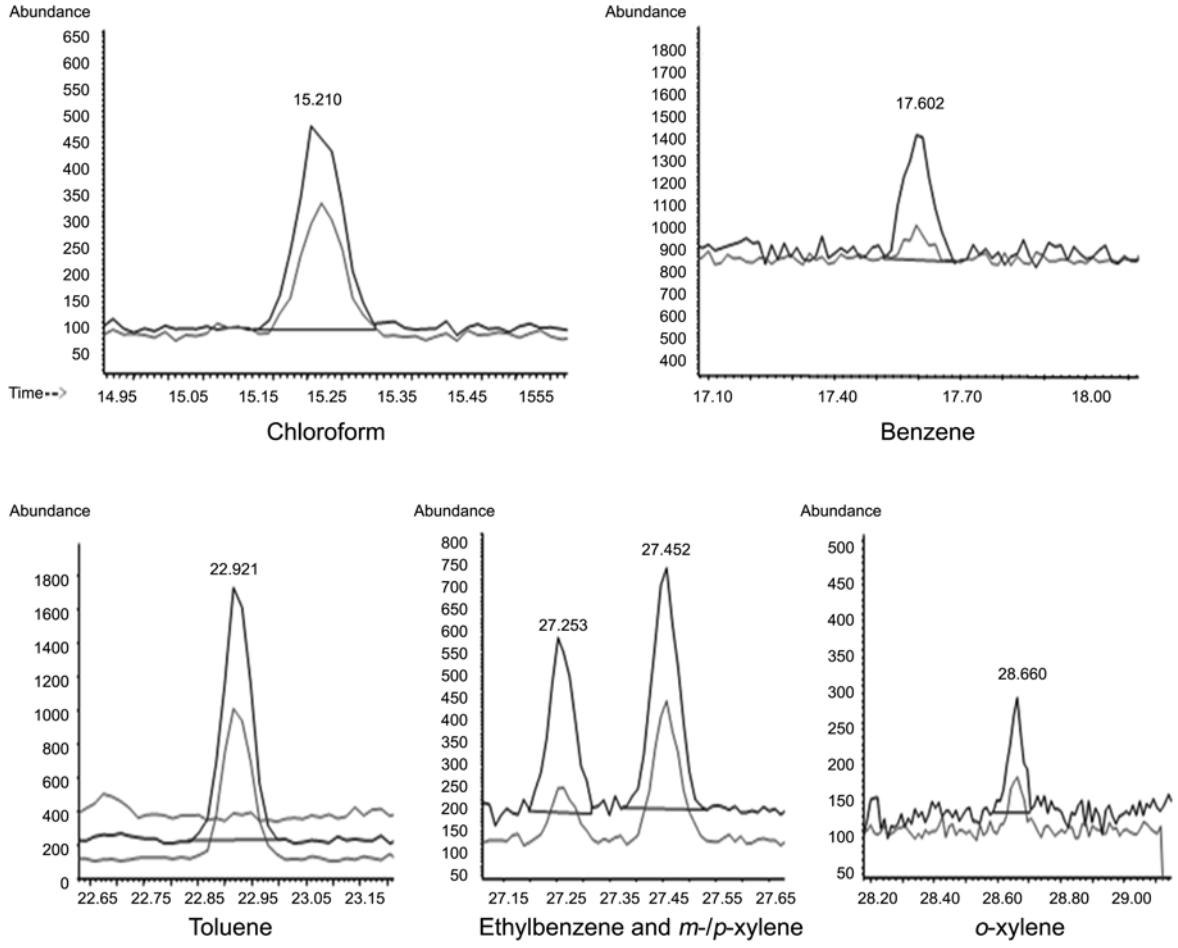

Figure 7. Extracted ion chromatograms of chloroform, benzene, toluene, ethyl-benzene and xylenes in real samples using HS method.

South Korea were assessed by HS. Nine hundred subjects: 300 from an industrial area, 300 from control site A (near industrial area) and 300 from control site B (far industrial area), participated in this study. Blood samples were immediately analyzed or stored at 4 or −20 °C until analyzed by the optimized HS method. Figure 6 shows a typical chromato-

Table 7. Frequency and concentration range of each compound detected in real samples Unit: ng mL^{-1}

	Chloroform	Benzene	Toluene	Ethylbenzene	*m*-/*p*-Xylene	*o*-Xylene
Industrial site	43.3% (0.05-5.82)	70.3% (0.07-2.08)	62.7% (0.05-5.17)	73.7% (0.05-2.84)	71.0% (0.10-3.62)	19.3% (0.08-1.38)
Control A	42.7% (0.05-5.84)	62.7% (0.05-1.57)	92.0% (0.05-4.55)	97.3% (0.09-6.26)	98.7% (0.14-6.08)	55.3% (0.09-0.74)
Control B	14.0% (0.05-2.60)	7.7% (0.05-2.20)	97.3% (0.08-11.62)	51.0% (0.05-0.31)	48.7% (0.10-0.90)	37.3% (0.05-0.24)

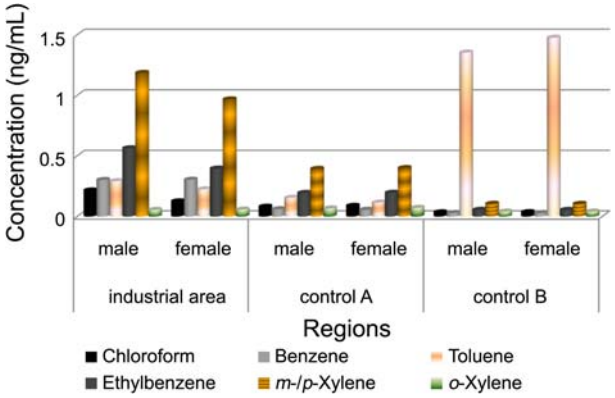

Figure 8. Comparison of six compounds according to sex distinction within three groups blood samples.

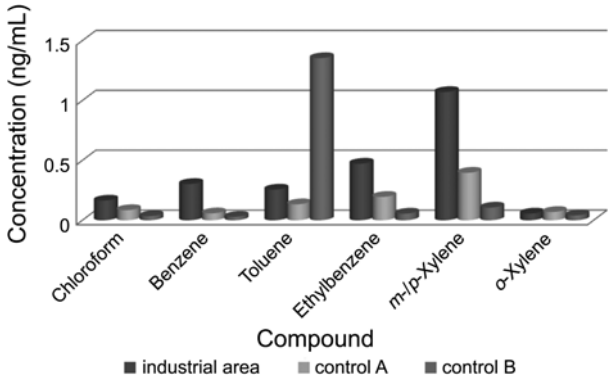

Figure 9. Geometric mean concentration of six compounds within three groups blood samples.

gram obtained from such blood samples by HS with final determination by GC-MS. Six compounds were detectable in the samples (Fig. 7).

Table 7 shows the frequency and concentration rang of each compound detected in samples from the industrial and control areas. Chloroform and benzene were frequently detected in the blood of inhabitants of the industrial site (chloroform in 43.3% and benzene in 70.3% of samples) > control A > control B region, with samples detected at wide concentration ranges (chloroform 0.05-5.82 ng mL^{-1} and benzene 0.07-2.08 ng mL^{-1} in industrial site). VOCs occurred differently in males and females (Fig. 8), though details of this difference were not available. The geomeans of each compound's concentration (chloroform 0.16 ng/mL, benzene 0.30 ng/mL, ethylbenzene 0.47 ng mL^{-1} and *m*-/*p*-xylene 1.07 ng mL^{-1}) in the blood from the industrial area were higher than those from the control sites, with the exceptions of toluene and *o*-xylene (Fig. 9).

Conclusions

HS was developed as a rapid and convenient extraction method to determine VOCs in whole blood. It was shown to be suitable for qualitatively and quantitatively determining VOCs over a wide range of concentrations. Its precision of assessing VOCs in blood ranged from 1.35 to 8.27%; its accuracy ranged from −6.78 to 14.06%.

The developed HS method was more sensitive than HS-SPME for determining VOCs in blood samples by gas chromatography/mass spectrometry. It could also achieve results more quickly than HS-SPME.

The HS method was used to analyze VOCs in human blood samples collected from industrial and control areas of South Korea. VOCs' geomean concentrations were generally higher in the blood samples collected from industrial area than from the control areas, with the exceptions of toluene and *o*-xylene. Chloroform was found at 0.05 to 5.82 ng mL^{-1} in 43.3% of the samples from the industrial site; benzene was found at 0.07 to 2.08 ng mL^{-1} in 70.3% of the samples from the industrial area.

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