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Sensitive headspace gas chromatography–mass spectrometry determination of trihalomethanes in urine

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Abstract

A sensitive and straightforward method for the determination of trihalomethanes (THMs) in urine by using headspace extraction technique has been developed. Chemical and instrumental variables were studied in order to optimize the method for sensitivity: an excess of KCl (4 g per 12 ml of urine), an oven temperature of 85 °C and an equilibration time of 30 min were selected. The use of the mass spectrometer in selected ion monitoring mode allows achieving linear ranges between 10 and 5000 ng/l and detection limits from 3 to 10 ng/l, for 12 ml of urine. The stability of the urine sample during storage at 4 and −20 °C was also evaluated: THMs remained stable for up to 2 days and 2 months, respectively. Finally, the method was successfully applied to study the THM uptake from swimmers of an indoor swimming pool, as well as non-swimmers. This study revealed that the concentrations of THMs in urine increased approximately three times for chloroform and bromodichloromethane after swimming activity. In addition, THMs in unchanged form were mainly excreted within 2–3 h after the end of exposure.

Keywords: Headspace technique; Trihalomethanes (THMs); Swimming pools; Urine sample; Exposure

1. Introduction

Nowadays, chlorination is the most widely used technique for disinfection of drinking water [1]. However, scientists discovered that chlorination of organic matter in fresh water resulted in formation of disinfection by-products (DBPs), including a variety of chlorinated compounds. Among these DBPs, trihalomethanes (THMs: chloroform, bromodichloromethane, dibromochloromethane and bromoform), have been recognized as carcinogenic halogenated by-products and potentially hazardous to human health [2]. Several epidemiological studies have been performed to investigate the correlation between chlorination of drinking water and cancer mortality [3]. The results of animal studies have demonstrated that bromodichloromethane causes more persistent liver toxicity and is slightly more toxic to the kidney at lower doses than chloroform [4]. In addition, some experimental studies about the association between adverse reproductive and development effects and exposure to these compounds have been reviewed [5,6]. Drinking water, apart from drinking, is also used for cooking, showering, bathing, and similar activities. Swimming pool water must be disinfected to avoid microbial growth and to keep swimmers from infections, since organic materials of various forms (perspiration, urine, mucus, skin particles, hair, lotion, etc.) are released into swimming pool water by swimmers. If residual chlorine exists in the water distribution system, formation of THMs continues as much time as organic matter is present and until the free chlorine supply is exhausted [7]. The levels of THMs in swimming pool waters showed a tendency of wide variation (20–150 ng/ml) [7,8], and were higher than levels found in drinking water (1–50 ng/ml) [9]; therefore swimmers have a potential risk of exposure not only by ingestion but also through contact with the skin (dermal absorption) and by inhalation [10].

For many years the biomarkers used for the biological monitoring of subjects occupationally exposed to volatile organic compounds (VOCs) have been final metabolites; however, metabolites have insufficient specificity. On the other hand, the urinary or blood concentrations of unchanged solvents are characterized by high levels of specificity, but they are unstable inside the matrix, on account of their volatility. The American Conference of Governmental Industrial Hygienists,

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among other Societies, includes in the biological limits for 2006 the urinary concentrations of several solvents, but not THMs [11]. Imbriani et al. have reviewed the state of the art of gases and organic solvents in urine as biomarkers of occupational exposure [12,13]. As a conclusion, they can claim that urinary excretion of unmodified solvents is a representative index of occupational exposure to solvents, even at low levels, and offers several advantages over other exposure indexes.

VOCs are arguably one of the most common organic chemicals to which humans are frequently exposed. In particular benzene, toluene, ethylbenzene and xylenes (BTEX) have been determined in urine of people exposed to these pollutants by headspace solid-phase microextraction (HS-SPME) and gas chromatography–mass spectrometry (GC/MS) [14], by purge and trap-GC/MS [15], and in blood and urine of people not occupationally exposed to BTEX, by HS-GC/MS [16]. Volatile chlorinated hydrocarbons have also been determined in biological fluids by HS-SPME-GC/MS [17,18] with detection limits 20 times lower than those obtained by static headspace; detection limits of 100 ng/l were obtained by using purge and trap-GC/MS [19], compared with static headspace this method is 100 times more sensitive. Chloroform in human urine was extracted by HS-SPME before GC/FID; however, the extraction efficiency was only of 57% and the detection limit 200 ng/ml [20]. Polkowska et al. have published more than ten articles about the determination of THMs in urine of exposed subjects [21,22] and the limits of detection were below 20 ng/l for all analytes [23]. The compounds were isolated in a complicate continuous system, which included two thin layer headspace columns; the condensate aqueous phase containing the volatile analytes was analyzed by direct aqueous injection-gas chromatography with electron capture detection. The presence of unchanged forms of these compounds in urine (ca. 4–14% of the THMs input), pointing to an incomplete detoxification metabolism, might be a useful indicator of the exposure to these compounds [22]. THMs may accumulate in various tissues (e.g. bone, fat) and organs (e.g. brain, liver), and part of the input may be excreted in unchanged form or may be metabolized by biochemical transformations leading to carbon monoxide and phosgene. The metabolites are excreted in breath, urine or bile, being excretion through the kidneys the most important in higher organisms [22]. The exposure of swimming pools employees was estimated by the determination of THM concentrations in alveolar air [24] and in blood and exhaled breath samples as biomarkers of exposure to participants conducting 14 common household water use activities [25]. Cammann and Hubner [26] confirmed that exhaustive physical exercise is correlated with high concentrations of THMs in blood and urine.

An aspect not adequately evaluated to date is the exposure to THMs of swimmers in indoor swimming pools, who are exposed by inhalation, ingestion and dermal contact. The aim of this study was to develop a sensitive and straightforward method for the THM determination in urine by headspace-GC/MS, and then apply this method to the evaluation of the THM concentrations in swimmers urine.

2. Experimental

2.1. Chemicals and standards

Chloroform, bromodichloromethane, dibromochloromethane, bromoform, and fluorobenzene (internal standard, IS, recommended for its use in the determination of THMs [7]) were purchased from Sigma-Aldrich (Madrid, Spain); methanol, acetone and potassium chloride were supplied by Merck (Madrid, Spain). Stock standard solutions were prepared at concentrations of 1.0 mg/ml in methanol and stored in amber glass stoppered bottles (without headspace) at 4 °C up to 3 months. Intermediate standard solutions were prepared fortnightly by diluting aliquots of stock solutions in methanol and stored in the dark at 4 °C. Working standards were prepared at the nanogram per liter level by spiking known amounts of the stocks into 20 ml glass vials containing the blank urine. The urine used for the preparation of these solutions was a pool of urine from volunteers who only consumed mineral water, free from THMs.

2.2. Gas chromatographic system and conditions

Separations were carried out by using an HS autosampler HP 7694 and an HP 6890 gas chromatograph (Agilent Technologies, Palo Alto, CA) equipped with an HP 5973 mass selective detector. The autosampler consists of an oven to heat the samples and a carousel (with capacity for 44 vials) equipped with a robotic arm to place the vials inside the oven; also, the HS sampler included a 3 ml loop connected to a six-port injection valve and an inert transfer line. Helium (5.5 grade purity, Air Liquid, Seville, Spain), regulated by a digital pressure and flow controller, was used both to pressurize the vial and transfer the loop content to the injection port of the gas chromatograph, which was equipped with a crosslinked HP-5MS [(5%)-phenyl-(95%) methylpolysiloxane] capillary column (30 m × 0.25 mm i.d., 0.25 μm film thickness, J & W Scientific, Cromlab, Barcelona, Spain). Sample injection was done in split mode (1:35 split ratio) with an inlet temperature of 250 °C. Mass spectra were obtained at 70 eV in the electron impact ionization mode. The source and quadrupole temperatures were maintained at 230 and 150 °C, respectively. Total ion current chromatograms were acquired and processed using G1701DA (rev. D.01.02) MSD Productivity ChemStation software (Agilent Technologies).

Helium was maintained at a flow-rate of 1 ml/min by using electronic pressure control. The chromatographic oven temperature programme was as follows: 40 °C, hold 3 min, 15 °C/min to 95 °C with a 2 min hold, then 25 °C/min to 200 °C and hold for 3 min. The chromatographic run was complete in 16 min. A solvent delay of 2.2 min was set to protect the filament from oxidation. Initial screening of samples was conducted in total ion chromatography (TIC) mode between *m/z* 45 and 255 at 6.5 scans/s. Quantification of THMs was performed in selected ion monitoring (SIM) mode, and three different acquisition windows were defined taking into account the retention times and suitable fragments of THMs, as shown in Table 1. All the scans were performed in high resolution mode and with a dwell time of 100 ms.

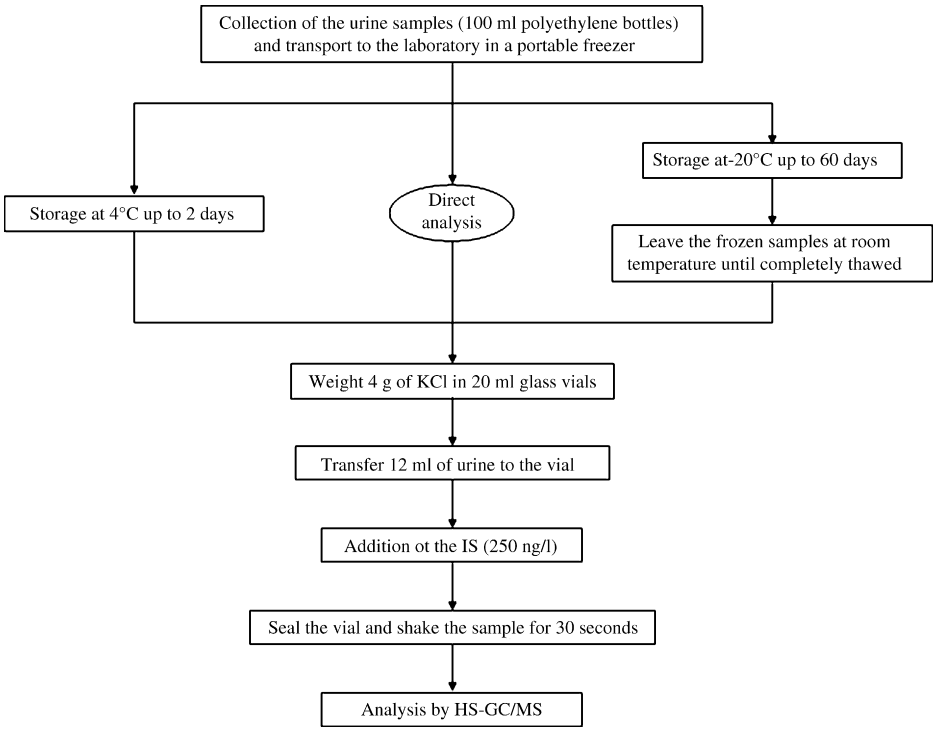

Fig. 1. Flow diagram representing the whole analytical protocol.

2.3. Urine samples

Urine samples were kindly supplied by swimmers of an indoor swimming pool and by non exposed volunteers. During the time in which the study was carried out, all subjects consumed only mineral water, free from THMs.

Samples were collected 5–10 min before and after the bath activity in sterilized polyethylene bottles of 100 ml (with hermetical close) without headspace to prevent the formation of air bubbles, and were collected in an area separated from the site of exposure in order to avoid the risk of contamination. Urine samples were transported to the laboratory in a portable freezer and immediately analyzed after collection or stored at 4 °C up to 48 h. When the time between sample collection and analysis exceeded 48 h, samples were stored at −20 °C up to 60 days as maximum to avoid storage losses. The frozen samples were left at room temperature until completely thawed. After gentle mixing, urine was transferred into the analysis vials. The whole procedure followed in this work is schematically shown in Fig. 1.

Samples were placed in 20 ml glass flat bottomed vials, with 20 mm PTFE-silicone septa caps and a crimped aluminum closure (Supelco, Madrid, Spain). Vials and septa were heated at 100 and 70 °C, respectively, overnight prior to use.

2.4. Experimental procedure

As depicted in Fig. 1, 12 ml of urine or blank urine sample containing between 10 and 5000 ng/l of each THM were transferred, by means of a syringe, into a 20 ml glass vial containing 4 g of KCl. An excess of KCl was added to saturate the sample. Fluorobenzene (IS) was also spiked to the sample at a level of 250 ng/l and the analysis vial was tightly sealed. Samples were analyzed by HS-GC/MS, using the following operating conditions for the HS autosampler: vial equilibration time, 30 min; oven temperature, 85 °C; vial pressurization time, 30 s; loop temperature, 100 °C; loop fill time, 12 s; transfer line temperature, 110 °C. Each standard or sample was analyzed in triplicate. The concentrations of analytes were automatically calculated by relating to previously created calibration curves, where the peak area ratios (sample/IS) were plotted as a function of the sample concentration.

Table 1
Identification/quantification conditions for THMs in urine

Compound	Retention time (min)	Time interval (min)	Selected ions for identification (*m/z*)[a]
Chloroform	3.2		**83**, 85, 47
Fluorobenzene	3.8	2.2–5.0	**96**, 70, 50
Bromodichloromethane	4.2		**83**, 85, 129
Dibromochloromethane	5.7	5.0–6.5	**129**, 127, 208
Bromoform	7.3	6.5–8.0	**173**, 171, 175

[a] In bold, ion chosen for quantification.

3. Results and discussion

3.1. Optimization of chemical and instrumental variables

For the study of chemical parameters, a spiked urine sample containing 12 ml of blank urine free of THMs (as occasionally chloroform was found in this blank at concentrations of 10–50 ng/l, the chloroform signal was corrected in the analytical signal of the urine standards), 25 ng of each THM and the internal standard (fluorobenzene), in 20 ml glass vial, was prepared. The effect of the addition of salt was firstly studied. Addition of salts may result in the change of the vapor and partial pressure, solubility, thermal conductivity, density, surface tension, etc. of each compound. These changes, if occurred, will result in the variation of the vapor/liquid equilibrium system [27]. Varying amounts of KCl between 0 and 4 g (amount that provides the saturation of the sample) were added to 12 ml of spiked blank urine samples. The abundance signal increased for all THMs when the salt amounts were increased as showed in Fig. 2. Compared to unsalted samples, relative recovery of salted (4 g of KCl) samples was 2.1 times greater for $CHCl_3$ and 1.9 times greater for $CHBrCl_2$, $CHBr_2Cl$ and $CHBr_3$. A concentration of 4 g of KCl per 12 ml of urine (saturated solution) was selected as working value in order to homogenize urine samples since they contain different values of ionic strength [17]. On the other hand, saturated urine samples can hinder the extraction of THMs from the liquid to the gas phase by partial sorption of the analytes on the salt. Therefore, a complementary study was carried out in order to establish any possible loss of analytes by partial sorption on the insolubilized salt. For this purpose, saturated blank urine samples spiked with each THM were stored at 4 °C and analyzed at 0, 1, 3, 5, 8, 12, 24, and 48 h after their preparation. The obtained results showed that up to 8 h after spiking, the analytical signal for all THMs remained constant, and then a slightly decrease was observed (ca. 5–10%) probably owing to the partial sorption of THMs on the salt. For this reason, urine samples were saturated before their analysis. The effect of the urine solution pH on the THM extraction was studied over the range 1–12 by adjusting the urine solution with dilute HCl or NaOH as required. The signal abundance of all THMs remained constant up to a pH value of 9 and decreased slightly above this value. Otherwise, the addition of increasing amounts of acid has been reported in the literature as modifier to improve the VOC extraction from urine samples [28]. For this reason, the effect of HCl addition on the extraction of THMs from the spiked blank urine sample was studied up to 1.8 ml of concentrate HCl (final concentration in 12 ml of urine, 1.5 M); however, no positive effect on the THM extraction was observed. Therefore, the addition of acid solution was unnecessary taking into account that the addition of potassium chloride is sufficient.

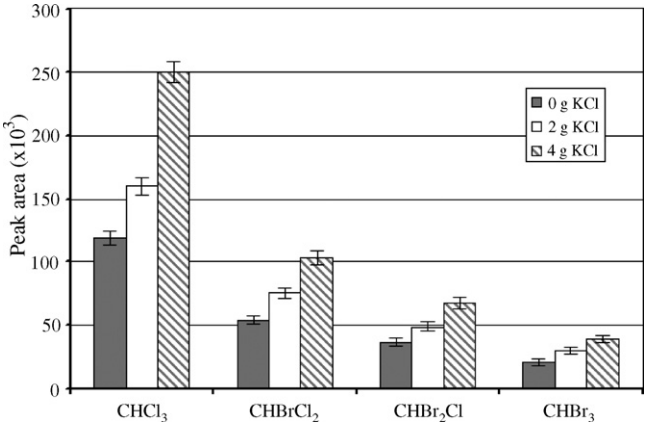

Fig. 2. Effect of the addition of salt on extraction of THMs. Error bars are the standard deviation for four measurements.

The instrumental variables of the headspace autosampler were also studied obtaining that oven temperature and vial equilibration time were the most influential parameters on the THM extraction. The effect of the oven temperature was checked from 70 to 90 °C using a vial equilibration time of 20 min, resulting in an increase of the analytical signal of all THMs with the oven temperature. An oven temperature of 85 °C was so selected as working value in order to minimize the evaporation of water. The vial equilibration time was studied from 10 to 40 min by using an oven temperature of 85 °C; the signal abundance increased when increasing the equilibration time up to 30 min (above which remained constant). Therefore, a vial equilibration time of 30 min was chosen as optimal value. Pressurization times between 15 and 45 s caused negligible changes in abundance signal for all THMs and thus, a pressurization time of 30 s was selected as working value.

3.2. Linearity, LOD and repeatability

The performance and reliability of the proposed method was assessed by determining the regression equation, sensitivity (defined as the slope of the calibration graph), limit of detection (LOD), linear range and precision for the compounds assayed. For this purpose, the mass spectrometer operating conditions were optimized in order to achieve the highest sensitivity (lowest LOD). The selection of fragments (*m*/*z*) from the mass spectra for the detection of each THM was performed in full scan mode (45–255 amu) following abundance and specificity criteria. Later, the MS was set in SIM mode to reach higher sensitivity and selectivity. The mass analyzer in SIM mode was operated in such a way that alternatively acquires only the ionic masses of interest; thus, the detection time for the ions of interest was increased and an improvement of the sensitivity in ca. 100 times was also observed. The ions monitored to identify and quantify each analyte are listed in the Table 1 as well as their retention times. For calibration, different volumes of a few microliters of standard solutions, containing all THMs at variable concentrations in methanol, were spiked to blank urine volumes of 12 ml saturated with KCl. Fluorobenzene (IS) was also added, at a concentration of 250 ng/l, in order to check that there were no problems with the needle of the autosampler, the carrier flow, the split injection and the extraction of the different compounds. A calibration curve for each THM, at concentrations ranging between 10 and 5000 ng/l was constructed by plotting the analyte-to-IS peak area ratio against the analyte concentration. The figures of merit of the proposed method, listed in Table 2, shows regression equations, LODs (expressed

Table 2
Analytical figures of merit of the determination of THMs

Compound	Regresion equation[a]	LOD (ng/1)	Linear range (ng/1)	R.S.D., $n = 11$ (%)	
				Within-day	Between-day
Chloroform	$Y = 73 \times 10^{-4} + 16 \times 10^{-4} X$	3	10–5000	3.5	4.2
Bromodichloromethane	$Y = 3 \times 10^{-4} + 10 \times 10^{-4} X$	4	15–5000	4.2	4.8
Dibromochloromethane	$Y = 14 \times 10^{-4} + 6 \times 10^{-4} X$	7	20–5000	4.4	5.2
Bromoform	$Y = 27 \times 10^{-4} + 3 \times 10^{-4} X$	10	30–5000	5.4	5.8

[a] Y = analyte area-to-internal standard area, X = concentration (ng/1).

as three times the regression standard deviation divided by the slope of calibration graphs), linear ranges (limit of quantification for each compound was taken as the lowest concentration in the linear range), and relative standard deviations (R.S.D.), obtained through the measure of eleven samples containing 200 ng/l of each THM and expressed as within-day and between-day precision.

3.3. Study of THM stability in urine

The critical steps in the definition of a procedure suitable for the biological monitoring of the environmental exposure to VOCs are the collection and handling of samples, during which contamination and/or loss of analytes could occur. A thorough study has been performed on two pools of urine specimens from exposed (swimmers) and unexposed (free of THMs) volunteer people. Urines from unexposed people were spiked with microliters of a methanolic solution of THMs in order to obtain a final concentration of 2 ng/ml of each compound in the urine sample. Spiked urine samples and urines from exposed people were stored in 100 ml polyethylene bottles at 4 or at −20 °C before the analysis. Analyses were carried out between 0 and 60 days after both types of urine were stored at 4 or at −20 °C, by using the procedure described in the Section 2.4. The obtained results showed that, in all instances, negligible differences in the stability were found between spiked urine samples and urines from exposed people (which only contained chloroform and bromodichloromethane). THM concentrations of urine samples (spiked and from exposed people) stored at 4 °C remained constant up to 2 days, after what the concentrations of all THMs decreased slightly as increasing the storage time up to 14 days, probably due to volatilization/degradation of the analytes. Therefore, THMs in the urine samples are stable in the storage at 4 °C only 2 days. On the other hand, little fluctuations around the mean value of the THM concentration with time was observed in all the urine samples (spiked and from exposed people) stored at −20 °C for the 2 months of the study. Based on these results, urine samples were collected in polyethylene bottles, transported to the laboratory in a portable freezer and stored at 4 °C up to 2 days or at −20 °C up to 60 days before their analysis.

3.3.1. Analysis of urine samples

The proposed method was applied to evaluate the exposure to THMs in indoor swimming pools and the uptake in swimmers. Twenty subjects, including 12 swimmers and eight non-swimmers, have participated in this study. Samples were collected as described in Section 2.3. and were immediately analyzed or stored at 4 or at −20 °C until their analysis. Sample preparation was made as explained in Section 2.4. The optimum

Table 3
Determination of THMs in urine samples by HS-GC/MS

Subject	Concentration found (ng/l)[a]			
	$CHCl_3$		$CHBrCl_2$	
	Before the bath	After the bath	Before the bath	After the bath
Swimmer 1	421 ± 21	1283 ± 65	18.6 ± 1.0	68.8 ± 3.6
Swimmer 2	492 ± 25	1525 ± 77	22.6 ± 1.2	76.8 ± 4.1
Swimmer 3	406 ± 20	1217 ± 62	17.7 ± 1.0	60.2 ± 3.3
Swimmer 4	542 ± 27	1573 ± 77	24.0 ± 1.3	79.2 ± 4.2
Swimmer 5	510 ± 26	1503 ± 78	23.4 ± 1.3	72.5 ± 3.8
Swimmer 6	413 ± 21	1279 ± 64	18.8 ± 1.0	65.8 ± 3.6
Swimmer 7	427 ± 21	1303 ± 67	18.9 ± 1.0	64.3 ± 3.5
Swimmer 8	444 ± 23	1331 ± 67	19.9 ± 1.1	61.4 ± 3.4
Swimmer 9	482 ± 24	1373 ± 68	21.3 ± 1.2	85.2 ± 4.5
Swimmer 10	430 ± 22	1377 ± 71	19.1 ± 1.0	68.8 ± 3.7
Swimmer 11	502 ± 25	1606 ± 80	23.0 ± 1.3	91.6 ± 4.9
Swimmer 12	408 ± 21	1265 ± 65	18.4 ± 1.0	68.4 ± 3.6
Non-swimmer 1	410 ± 22		17.0 ± 1.0	
Non-swimmer 2	486 ± 24		20.5 ± 1.2	
Non-swimmer 3	548 ± 27		21.8 ± 1.2	

[a] ±Standard deviation, $n = 5$.

time for the urine collection was studied in all the swimmers collecting spot samples of all their micturitions, at intervals of 1 h, during whole days of exposure. In addition, volunteers only consumed mineral water, which was THM-free, during the study. In all instances, the highest concentrations of THMs in urine were found immediately after the bath, so sampling was made approximately 5–10 min before and after the bath activities. The average time of the baths was 1 h approximately. THMs removed in unchanged form in urine were thorough excreted 2–3 h after the end of exposure. Only chloroform and bromodichloromethane were detectable in the samples collected (other THM compounds were probably present but at concentrations lower than the detection limits); their concentrations in swimmers urine before and after the bath are shown in Table 3. Urinary chloroform concentrations of non swimmers varied from 410 to 550 ng/l, and bromodichloromethane concentrations were between 17 and 22 ng/l (see Table 3), associated to common household water use activities, including ingestion of hot and cold tap water beverages, showering, clothes washing, hand washing, bathing, dish washing, and indirect exposure [25]. Both intervals were similar than those found in swimmers before the bath, as can be seen in Table 3. An increase of approximately three times in chloroform levels and of 3–4 times in bromodichloromethane levels can be observed in samples after exposure.

4. Conclusions

The proposed method is more sensitive than others described in the literature for the determination of THMs in waters by gas chromatography; thus, using headspace and SPME techniques, these analytes can be determined at concentrations from 0.1 to 75 ng/ml and from 0.05 to 80 ng/ml, respectively [27]. The unique method described in the literature about the determination of THMs in urine samples [21–23] is more sensitive (LODs ranged from 1 to 3 ng/l) than the method proposed in this paper (LODs ranged from 3 to 10 ng/l; 12 ml of urine), but it used volumes of urine from 150 to 250 ml, which were preconcentrated using thin layer headspace technique. Otherwise, the study carried out with exposed people to THMs during the swimming activity (swimmers) and unexposed people have shown up that the method has a great potential for the analysis of urine samples, even at very low concentrations.

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