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Article

Evaluation of Simulant Migration of Volatile Nitrosamines from Latex Gloves and Balloons by HS-SPME–GC–MS

Di Feng, Luo Liu, Liyuan Zhao, Qingfeng Zhou and Tianwei Tan*

Beijing Key Laboratory of Bioprocess, College of Life Science and Technology, Beijing University of Chemical Technology, Beijing, China

*Author to whom correspondence should be addressed. Email: twtan@mail.buct.edu.cn

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Nitrosamines are a group of carcinogens that have been found in various latex products. Methods have been developed for extraction, concentration and detection of simulant migration of volatile nitrosamines from latex gloves and balloons. After glove samples or balloon samples were treated with artificial sweat and artificial saliva, headspace solid-phase microextraction and gas chromatography with mass spectrometer detection were performed. Eight volatile nitrosamines were extracted by a fused silica fiber coated with carboxen-polydimethylsioxane, and solid-phase microextraction conditions were optimized. The developed method was successfully used to analyze simulant migration of volatile nitrosamines from latex gloves and balloons. The described methods are rapid and simple, with adequate sensitivity and without organic solvent.

Introduction

Several laboratories view most *N*-nitrosamines as genotoxic carcinogens to animals and humans. Exposure to nitrosamines in the general population occurs in different sources, such as food, tobacco, cosmetics and rubber products (1–4). Migration of nitrosamines from various latex products; e.g., nipples, condoms, gloves and balloons has been the focus of recent attention (3–9). Nitrosamines are brought into rubber products during vulcanization steps as a result of the nitrozation of secondary aminated vulcanization accelerators with nitrogen oxides in the industrial atmosphere and/or nitrites of uncertain origin (10). Nitrosamines migrate to the surface of rubber products during storage and usage. The standard EN12868 for nitrosamine migration from rubber teats (11) and the ISO committee draft for nitrosamine migration from condoms (12) have been established. The European directive 93/11/EEC regulated that the release of nitrosamines from teats and soothers should not exceed 10 μg/kg of material (13).

Latex gloves include usually sterile gloves, examination gloves and household gloves. In view of their close contact with skin, body fluids and tissues, it is also necessary to evaluate the release of nitrosamines from latex gloves. However, there is no international standard method or prescribed limits for nitrosamine migration from latex gloves. In 2009, a study was reported on detection and toxicity assessment of nitrosamine migration from latex gloves in the Chinese market (7). After treatment with artificial sweat (pH 5.5) for 4 h at 37°C, samples were analyzed by liquid–liquid extraction and gas chromatography–thermal energy analyzer (GC–TEA). *N*-Nitrosodimethylamine (NDMA), N-nitrosodiethylamine (NDEA) and N-nitrosodibutylamine (NDBA) were detected and the levels of nitrosamine migration from all 27 samples exceeded 10 μg/kg. In Germany and the Netherlands, it has been shown that nitrosamines were released when children's latex balloons were treated with artificial saliva for 1 h at 40°C to simulate the conditions of blowing up balloons by mouth (6, 9). According to BgVV Recommendation XXI (Germany), nitrosamine migration from balloons should comply with the following guidance values: 10 μg/kg *N*-nitrosamines (14). Nitrosamines released from the balloons collected from German markets in 2001 ranged from <10 to 380 μg/kg and 81% of 16 analyzed balloons were above the German recommendation (6). For the Dutch market in 2002, 86% of 57 analyzed balloons exceeded the limit (9).

In all known standards for determining the migration of nitrosamines from rubber products, nitrosamines are detected by traditional liquid–liquid extraction with methylene chloride and GC–TEA after samples are treated with artificial fluids. The procedures are time-consuming and labor-intensive and require toxic solvents. Solid-phase microextraction (SPME) is an organic solvent-free process that combines sampling, extraction, concentration and sample introduction in a single step. SPME has been shown to be a highly sensitive and selective technique that has successfully been applied to the extraction of volatile nitrosamines in water and foods (15–19). Furthermore, although TEA is a specific analyzer for nitrosamines (9, 11, 12), mass spectrometry (MS) detection is more universal in laboratories, which not only allows the analytes present in the sample to be quantified and detection, but also to be identified based on their structure.

However, the detection for volatile nitrosamine migration from latex products by the SPME-GC–MS method has not yet been investigated. The aim of this study was to optimize and apply the SPME technique to analyze volatile nitrosamine migration from nature latex gloves and balloons.

Materials and Methods

Reagents

The eight reference standards of NDMA, NDEA, NDBA, *N*-nitrodipropylamine (NDPA), *N*-nitrodiisopropylamine (NDiPA), *N*-nitrosopiperdine (NPIP), *N*-nitropyrrolidine (NPYR), and *N*-nitrosomorpholine (NMOR) were purchased from Chemservice (Westchester, PA) in methanol solvent. The standards were stored in amber vials in a refrigerator at 4°C. Methanol was 99.9% HPLC grade.

The artificial sweat was prepared according to the German 35 Method 82.10 (standard for the determination of

colorfastness for toys with artificial sweat) (20): 4.5 g sodium chloride, 0.3 g potassium chloride, 0.3 g sodium sulfate, 0.4 g ammonium chloride, 3.0 g lactic acid and 0.2 g urea were dissolved in 1 L distilled water. To simulate the pH of actual sweat, the pH was adjusted to pH 5.5 by adding 0.1M hydrochloric acid solution or 0.1M sodium hydroxide solution.

The artificial saliva was prepared as described by the EN12868 method (11): 4.2 g sodium hydrogen carbonate, 0.5 g sodium chloride, 0.2 g potassium carbonate and 30 mg sodium nitrite were dissolved in 1 L distilled water. The pH was adjusted to pH 9.0.

All reagents used to prepare artificial sweat and saliva were of analytical grade and obtained from Beijing Chemicals Factory (Beijing, China). The artificial sweat and saliva could be stored in a refrigerator at 4°C for one week.

Sample preparation and analysis

Seven different brands of latex balloons and 13 latex gloves, including two sterile gloves, two examination gloves and nine household gloves, were purchased randomly from the local market of Beijing in 2010. Samples were cut into pieces of approximately 0.5 cm^2. Optimization and method evaluation were carried out using non-nitrosamine latex gloves and balloons by spiking appropriate amounts of the diluted working standard solutions. Glove E01 and Balloon B07 were used as blank latex product samples because they contained no detectable level of target nitrosamines, according to the conventional liquid–liquid extraction technique with dichloromethane described by EN12868.

SPME equipment

An SPME holder and fused silica fiber coated with carboxen–polydimethylsiloxane (CAR–PDMS, 75 μm) were used to perform the experiments. All SPME equipment was purchased from Supelco (Bellefonte, PA). The fiber was conditioned according to the instructions provided by the suppliers.

GC–MS

Analysis was performed with a Shimadzu QP 2010 series gas chromatograph (Shimadzu; Kyoto, Japan) coupled to a mass selective detector (Shimadzu QP 2010). Chromatographic separation was carried out by 14% cyanpropylphenyl–86% dimethyl polysiloxane bonded phase fused silica capillary column (Rtx 1701; 30 m × 0.25 mm i.d. and 0.25 μm film thickness) (Restek, Bellefonte, PA). The flow rate of helium was 1.0 mL/min. The injector port was in splitless mode and temperature was 250°C. The column temperature for Rtx 1701 was programmed in two steps from 60°C (held 2 min) to 120°C at a rate of 15°C /min to 200°C at 8°C /min.

The transfer line and MS detector were maintained at 280 and 250 °C, respectively. The mass spectra were obtained by electronic impact at 70 eV and data collection at a rate of 0.2 scan/s. Detection of compounds was carried out in selected ion monitoring (SIM) mode. The following m/z values were selected for each compound (the base peaks used for quantification are in bold): NDMA 42, 43, **74**; NDEA 42, 44, **102**; NPYR 41, 42, **100**; NMOR 56, 86, **116**; NPIP 42, 55, **114**; NDBA 57, **84**, 158; NDiPA and NDPA 43,70, **130**.

SPME extraction of volatile nitrosamine migration from gloves and balloons

Samples of approximately 2 g, 10 mL artificial sweat/saliva and a magnetic stir bar were placed into 20-mL amber open-top vials with septa. For migration of nitrosamines from gloves, the vial was placed on a heater/magnetic stirrer in a water bath for 4 h at 37°C to simulate the actual use of latex gloves for four working hours (7). For migration of nitrosamines from balloons, the vial was placed on a heater/magnetic stirrer in water bath for 1 h at 40°C (6, 9). After the simulant migration of nitrosamines from glove samples and balloon samples, the septa were pierced by the SPME holder. The SPME fiber was immediately exposed to the sample headspace. After that, the fiber was retracted and removed. The extraction time and temperature were further optimized. The desorption procedure of the analyte from the fiber coating was performed at 250°C for 5 min and the chromatographic conditions employed were as described previously.

SPME optimization

Glove/balloon samples of approximately 2 g, fortified with 200 ng each of nitrosamine standard, 10 mL distilled water, and a magnetic stir were placed into the vial. After migration experiments of nitrosamines, the SPME extraction was carried out as described previously, and the extraction temperature (37, 45, 60 and 80°C) and extraction time (20, 45, 60, 240 and 700 min), respectively, were optimized.

Method evaluation

The method linearity was evaluated by plotting calibration curves of the obtained response areas versus the concentration of the nitrosamines added to the latex gloves and balloons with concentrations ranging from 10 to 200 ng/g in samples, to simulate the reported level of migrating from latex products in Chinese market (7, 8); meanwhile, these external standards provided a five-level calibration range from 10 to 200 ng/g. The limits of detection (LOD) for nitrosamines were defined as the concentration of nitrosamines in samples that caused a peak with a signal-to-noise ratio (S/N) of 3. To evaluate the accuracy of the method, recovery studies were preformed for eight nitrosamines using three spike levels (20, 50 and 100 ng/g) for each nitrosamine. The entire procedure was carried out in triplicate and the average was used in calculations. The repeatability of the method (percent relative standard deviation; RSD) was evaluated by analyzing seven replicates at the same spike level (50 ng/g).

Results and Discussion

SPME optimization

SPME optimization of nitrosamine migration from gloves

After the gloves were treated with artificial sweat for 4 h at 37°C, the temperature of SPME was optimized. The results are

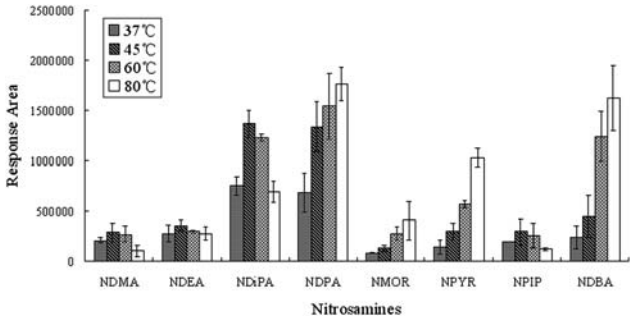

Figure 1. SPME temperature optimization of nitrosamine migration from Glove E01 into artificial sweat ($n = 3$, 2 g Glove E01 and 100 ng nitrosamine standard in 10 mL artificial sweat, 60 min extraction).

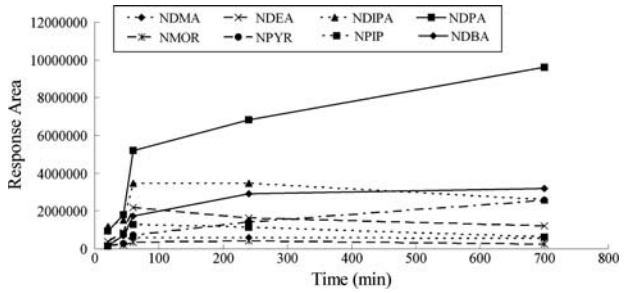

Figure 2. Extraction time for nitrosamine migration from Glove E01 into artificial sweat ($n = 3$, 2 g GloveE01 and 100 ng nitrosamine standard in 10 mL artificial sweat at 45°C).

presented in Figure 1. From 37 to 80°C, NDPA, NMOR, NPYR and NDBA showed a substantial increase in extraction efficiency. Between 37 and 45°C, NDMA, NDEA, NDiPA and NPIP showed an increase in response area; however, their response areas decreased at 60°C. The extraction of NDMA, NDEA, NDiPA and NPIP was most efficient at 45°C. Because NDMA, NDEA and NDBA are the primary nitrosamines that migrate from rubber products (5–9), 45°C was chosen as a compromise extraction temperature.

Various extraction times were evaluated to determine the necessary time for eight nitrosamines (Figure 2). The results showed that equilibrium was reached at 60 min of extraction for NDMA. For NDPA, NPYR and NDBA, the longer the extraction time, the higher the response areas. Even with a long extraction time (700 min), their equilibrium was not reached. The response areas of NDEA, NDiPA and NPIP increased until 60 min. After 60 min, their response areas decreased. Thus, the optimum extraction time was 60 min. However, the highest extraction efficient of NMOR presented an extraction time of 240 min. To pay more attention to NDMA, NDEA and NDBA than the other nitrosamines in this study, and in the interest of a more efficient analysis, lower labor costs and longer operation life of the SPME fiber, an extraction time of 60 min was chosen.

SPME optimization of nitrosamine migration from balloons

After balloons were treated with artificial saliva for 1 h at 40°C, the SPME optimization of nitrosamine migration from balloons was examined. The results of temperature effects are shown in Figure 3. NDiPA, NDPA, NPYR and NDBA showed a continuous increase in chromatographic area from 45 to 80°C. However,

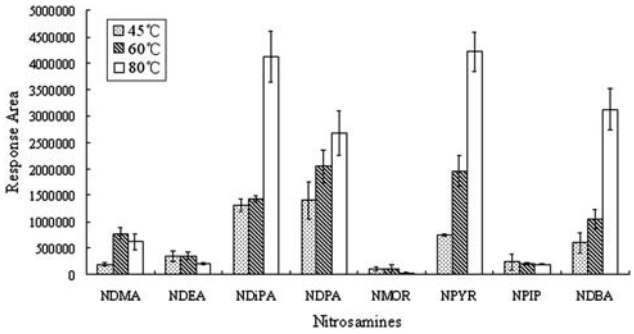

Figure 3. SPME temperature optimization of nitrosamine migration from Balloon B07 into artificial saliva ($n = 3$, 2 g Balloon B07 and 100 ng nitrosamine standard in 10 mL artificial saliva for 60 min).

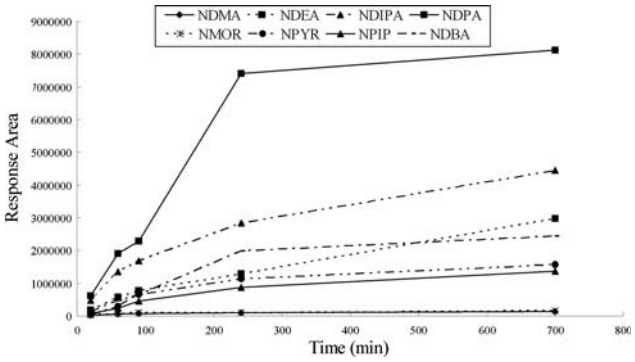

Figure 4. Extraction time for nitrosamine migration from Balloon B07 into artificial saliva ($n = 3$, 2 g Balloon B07 and 100 ng nitrosamine standard in 10 mL artificial saliva at 45°C).

the extraction of NDMA and NDEA showed the most efficiency at 60°C. Taking all factors into account, 60°C was chosen as a compromise extraction temperature.

Extraction times were also investigated to determine the necessary time for eight nitrosamines (Figure 4). The results showed that the longer the extraction time, the higher the response areas for all studied nitrosamines from 10 to 700 min. Therefore, the equilibrium was not reached for any of the studied nitrosamines until 700 min. For the same reason as for extraction time selection for nitrosamine migration from gloves, an extraction time of 60 min was chosen for further experiments.

Optimization of additional conditions

To pay more attention to NDMA, NDEA and NDBA than the other nitrosamines in this study, a CAR–PDMS fiber was used in this study. Considering possible migration from complex matrix of latex products (gloves and balloons) into artificial secretion (sweat and saliva), headspace extraction was applied. The speed of constant stirring was chosen to be 800 rpm to enable stable and homogeneous rotation for the samples and the magnetic stirrer. In addition, the optimization of salt concentration and pH of extraction solution was not performed, due to definitive ingredients and pH of artificial sweat and artificial saliva. Some extraction conditions, such as headspace volume and desorption condition, were used from data available in the literature (17, 18). Considering these factors

comprehensively, the primary optimizations of extraction temperature and extraction time were performed in this study.

Method evaluation

The chromatogram of the nitrosamine standard mixture is shown in Figure 5. The chromatogram of the blank sample (Glove E01) is shown in Figure 6. Significant separations of the nitrosamines were obtained in the Rtx1701 column. Under the established experimental conditions for the HS-SPME extraction and GC–MS detection, two methods were evaluated. The linear regression equation, regression coefficient (R^2), linear range, LOD, recovery values and RSD of the HS-SPME–GC–MS method for determination of nitrosamine migration from latex gloves into artificial sweat are presented in Table I. The R^2 ranged from 0.9158 to 0.9980 for all nitrosamines. All nitrosamines showed satisfactory LOD of 0.04–0.89 ng/g, which were lower than the limit of Directive 93/11/EEC established by European Union, which states that the migration of nitrosamines from teats and soothers should not exceed 10 ng/g (13). The average recovery of all nitrosamines ranged from 75.4% to 116.9%, which showed the satisfactory performance of the HS-SPME procedure and GC–MS separation. However, the repeatability of the method for NMOR, NPYR and NPIP with RSD from 11.2–21.1% was not very satisfactory, probably because of a disturbance from complex matrix in latex gloves. In 2009, research was reported on the detection of nitrosamine migration from latex gloves (7). After treatment with artificial sweat (pH 5.5) for 4 h at 37°C, samples were analyzed by liquid–liquid extraction and GC–TEA. The LOD for all nitrosamines varied between 1.0 and 9.5 ng/g sample. Recoveries ranged from 72% to 101% for NDMA, NDEA and NDBA with average RSD of 4–8%. Compared with traditional liquid–liquid extraction, the HS-SPME–GC–MS method is more rapid, simple, sensitive and solvent-free.

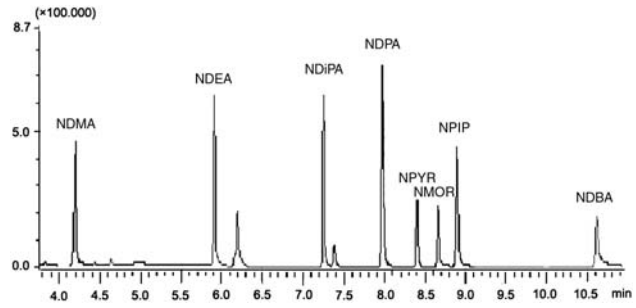

Figure 5. Chromatogram of a nitrosamine standard mixture (100 ng/mL) on an Rtx1701 column by GC–MS.

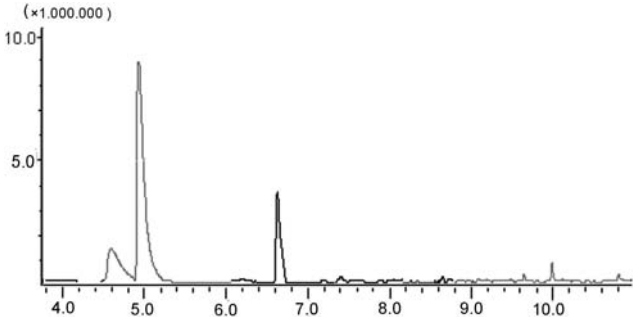

Figure 6. Chromatogram of the blank sample (Glove E01) detected by the HS-SPME–GC–MS method.

The previously described performance criteria of the HS-SPME–GC–MS method for the determination of nitrosamine migration from latex balloons into artificial saliva are shown in Table II. R^2 values were >0.99 for NDEA, NPIP and NDBA and >0.9 for NDMA, NDiPA and NDPA. NMOR and NPYR presented dissatisfactory R^2 values of 0.8150 and 0.8665, respectively, probably due to the poor repeatability. The LOD from 0.26 ng/g (NDiPA) to 5.38ng/g (NMOR) were lower than the limit of Directive 93/11/EEC and enough for detecting most of these chemicals at the commonly reported levels (7, 8). The recoveries of all nitrosamines were acceptable, ranging from 101.4 to 120.5%. The repeatability of some nitrosamines was dissatisfactory, probably owing to the impact of artificial secretions and complex matrix in latex balloons. In addition, the CAR–PDMA fiber had low sensitivity and worse repeatability results for NMOR, NPYP and NPIP than other reported types (17, 21).

Sample analysis

Nitrosamine migration from 13 latex gloves (including seven household gloves, three sterile gloves and three examination gloves) and seven balloons into artificial sweat and artificial saliva were detected by the HS-SPME–GC–MS method. Because of complex matrix in latex products and different compositions from different producers, and because the efficiency of HS-SPME is influenced by the matrix, the external standard method was used for quantitative analysis. The results are shown in Table III. NDMA, NDEA and NDBA were detected in 11 latex gloves and seven balloons. NDiPA, NDPA, NMOR,

Table I
Linear Regression Equation, R^2, LOD, Linear Range, Recovery and RSD for Determination of Nitrosamine Migration from Gloves into Artificial Sweat by the HS-SPME–GC–MS Method

	Equation	R^2	LOD (ng/g)	Linear range (ng/g)	Recovery (%)			Average recovery (%)	RSD (%)
					20.0 ng/g	50.0 ng/g	100.0 ng/g		
NDMA	$Y = 1991.4X + 4669.6$	0.9950	0.72	2.40–200	120.6	101.7	100.5	107.6	10.5
NDEA	$Y = 4484X - 10684$	0.9964	0.24	0.81–200	98.6	94.9	100.1	97.9	2.7
NDiPA	$Y = 11176X - 1503.2$	0.9980	0.04	0.15–200	92.4	100.6	99.9	97.6	4.7
NDPA	$Y = 4446.2X - 11514$	0.9956	0.26	0.87–200	91.2	98.6	98.8	96.2	4.5
NMOR	$Y = 133.08X + 26917$	0.9254	0.85	2.83–200	115.5	82.3	91.0	96.3	17.9
NPYR	$Y = 207.26X + 25068$	0.9158	0.89	2.98–200	84.5	59.4	82.3	75.4	18.4
NPIP	$Y = 800.91X - 792.52$	0.9815	0.09	0.29–200	127.6	120.8	102.2	116.9	11.2
NDBA	$Y = 528.71X + 5159.4$	0.9889	0.68	2.28–200	98.3	103.4	107.5	103.1	4.5

Table II
Linear Regression Equation, R^2, LOD, Linear Range, Recovery and RSD for Determination of Nitrosamine Migration from Balloons into Artificial Saliva by the HS-SPME–GC–MS Method

	Equation	R^2	LOD (ng/g)	Linear range (ng/g)	Recovery (%)			Average recovery (%)	RSD (%)
					20.0 ng/g	50.0 ng/g	100.0 ng/g		
NDMA	$Y = 2326.4X + 119848$	0.9725	1.34	6.7–200	113.1	106.6	104.6	108.1	11.1
NDEA	$Y = 3593.8X + 29869$	0.9993	0.96	4.8–200	112.8	106.8	101.5	107.0	2.9
NDiPA	$Y = 5401X + 831857$	0.9633	0.26	1.3–200	138.8	120	102.6	120.5	9.8
NDPA	$Y = 11841X + 113509$	0.9898	2.65	13.25–200	98.7	103.7	101.8	101.4	9.1
NMOR	$Y = 120.26X + 26471$	0.8150	5.38	26.9–200	116.4	119.8	107.6	114.6	15.9
NPYR	$Y = 1582.9 + 554721$	0.8665	0.90	4.5–200	126.8	110.7	113.2	116.9	13.2
NPIP	$Y = 1343.6 + 30153$	0.9915	0.70	3.5–200	119.1	93.9	108.5	107.2	13.7
NDBA	$Y = 3336.8X + 302543$	0.9970	0.63	3.15–200	107	108	93.9	103.0	5.8

Table III
Detection Results of Nitrosamine Migration from 13 Latex Gloves after Treatment with Artificial Sweat at 37°C for 4 h and Nitrosamine Migration from Seven Latex Balloons after Treatment with Artificial Saliva at 40°C for 1 h by the HS-SPME–GC–MS Method ($n = 3$)*

	Nitrosamines (μg/kg)								
	NDMA	NDEA	NDiPA	NDPA	NMOR	NPYR	NPIP	NDBA	Total
H01	—	9.92	—	—	—	—	—	1,909.31	1,919.23
H02	—	10.66	—	—	—	—	—	114.31	124.97
H03	23.02	12.80	—	—	—	—	—	57.00	92.82
H04	—	—	—	—	—	—	—	1,870.83	1,870.83
H05	—	301.95	—	—	—	—	—	—	301.95
H06	137.66	64.23	—	—	—	—	—	—	201.89
H07	—	21.88	—	—	—	—	—	—	21.88
E01	—	—	—	—	—	—	—	—	—
E02	151.99	—	—	—	—	—	—	269.10	421.09
E03	—	—	—	—	—	—	—	—	—
S01	—	—	—	—	—	—	—	219.94	219.94
S02	—	15.98	—	—	—	—	—	—	15.98
S03	—	7.74	—	—	—	—	—	104.52	112.26
B01	—	31.37	—	—	—	—	—	76.83	31.37
B02	25.58	55.27	—	—	—	—	—	—	157.68
B03	63.23	—	—	—	—	—	—	—	63.23
B04	75.64	—	—	—	—	—	—	70.86	75.64
B05	180.45	—	—	—	—	—	—	54.24	251.31
B06	151.72	131.76	—	—	—	—	—	—	337.72
B07	—	—	—	—	—	—	—	—	—

*Note: undetected compounds are indicated by a dash; S: sterile gloves; E: examination gloves; H: household gloves; B: balloons.

NPYR and NPIP were not detectable. The detection frequency of NDMA, NDEA and NDBA in 13 latex gloves was 23%, 62% and 62%, respectively. The migration level of NDMA ranged from 23.02 to 151.99 ng/g, NDEA from <10 to 301.95 ng/g and NDBA from 57.00 to 1,909.31 ng/g. Total nitrosamines varied from 15.98 to 1919.23 ng/g, respectively. In 2010, 85% of 13 sampled gloves released nitrosamines above the recommended limit in Directive 93/11/EEC. The highest migration level exceed approximately 192 times of the limit. Only two examination gloves (E01 and E03) complied with the migration limit with no detectable released nitrosamines. For example, an individual could be exposed to approximately 57.58 μg of nitrosamines after wearing the household glove sample H01 for 4 h (the total nitrosamine level of H01 was 1,919.23 ng/g and average weight of one H01 glove was 30 g).

The detection frequency of NDMA, NDEA and NDBA in seven latex balloons was 71%, 43% and 43%, respectively. The migration level of NDMA ranged from 25.58 to 151.72 ng/g, NDEA from 31.37 to 131.76 ng/g and NDBA from 54.24 to 76.83 ng/g, respectively. Total nitrosamines varied from 31.37 to 337.72 ng/g. Except for one latex balloon (B07) that complied with the migration limit, all other balloons released nitrosamines that were above the recommended level in Directive 93/11/EEC.

Conclusions

In this study, an analytical method was developed, evaluated and successfully used to detect migration of volatile nitrosamines from latex gloves and balloons. After migration experiments of nitrosamines in latex products, HS-SPME for extraction of the analytes, GC–MS instrument for detection and the external standard method for quantitative analysis were performed. Compared with traditional liquid–liquid extraction, the two methods are rapid, simple, solvent-free, adequately sensitive and selective. A high content of nitrosamine migration from latex gloves and balloons was found in this study. Of 20 sampled gloves and balloons, 85% released nitrosamines above the recommended limit in Directive 93/11/EEC, except for two examination gloves and one balloon that complied with the migration limit. Thus, more attention should be paid to nitrosamine migration from latex gloves and balloons. Furthermore, nitrosamines were also reported to be detected in balloons from German and Dutch markets. However, until now, no international standard method or prescribed limits have been imposed on nitrosamine migration from latex gloves. The method described in this study may contribute to establish an international standard method for detection of nitrosamine migration from latex products.

Acknowledgments

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