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Simple quantification method for *N*-nitrosamines in atmospheric particulates based on facile pretreatment and GC-MS/MS

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ABSTRACT

Nine *N*-nitrosamines (i.e., *N*-nitrosomethylamine, *N*-nitrosodiethylamine (NDEA), *N*-nitrosodimethylamine (NDMA), *N*-nitrosodi-n-propylamine (NDPA), *N*-nitrosomorpholine (NMor), *N*-nitrosopyrrolidine (NPyr), *N*-nitrosopiperidine (NPip), *N*-nitorosodi-n-butylamine (NDBA), and *N*-nitrosodiphenylamine (NDPhA) in atmospheric $PM_{2.5}$ collected in the fall season from an roadside site and a residential in Seoul, Korea have been analyzed using a newly developed method consisting of simple direct liquid extraction assisted by ultrasonication and subsequent quantification using a gas chromatography-triple quadrupole mass spectrometry (GC-TQMS). Excellent recovery values (92–100%) and method detection limits for the target compounds atmospheric PM samples could be achieved even without an evaporation step for sample concentration. The concentration of total *N*-nitrosamines in $PM_{2.5}$ was ranged from 0.3 to 9.4 ng m^{-3} in this study; NDMA, NDEA, NDBA, NPyr, and NMor in $PM_{2.5}$ were found to be the most frequently encountered compounds at the sampling sites. Since no industrial plant is located in Seoul, vehicle exhausts were considered major cause of the formation of nitrosamines in this study. The mechanisms how these compounds are formed and detected in the atmosphere are explained from the viewpoint of secondary organic aerosol. Considering the concentrations of *N*-nitrosamines and their associated potential health risks, a systematic monitoring of nitrosamines present in both ambient air and $PM_{2.5}$ including seasonal and diurnal variations of selected sites (including potential precursor sources) should be carried out in the future. The proposed sample pretreatment method along with the analytical method will definitely help us perform the monitoring study.

1. Introduction

The interest in atmospheric particulate matter (PM), especially $PM_{2.5}$ (PMs with a diameter (D_p) of <2.5 μm), has increased because of its potential adverse effects on human health. $PM_{2.5}$ lies within the respirable size range for humans, so it is regulated as an important air pollutant (WHO, 2006). Over the past decades, numerous studies have examined the chemical compositions of PM to assess their potential adverse impacts (Donaldson et al., 2001; Brook et al., 2009). As other solids, PM is consisted with inorganic and organic materials. The inorganic components of atmospheric PM, e.g., ammonium, sulfate, nitrate, and sea salt, have been well studied, leading to the development of reliable inorganic aerosol models (Wexler and Seinfeld, 1991; Zhao et al., 2011). On the other hand, although characterization of organic carbon in the PM has been extensively studied (Yang et al., 2011) and water soluble organic carbon (WSOC) in terms of total organic carbon quantified (Huang et al., 2012; Paraskevopoulou et al., 2014; Rajput et al., 2013), limited numbers of organic compounds present in PM are quantified, notably polycyclic aromatic hydrocarbons (PAHs) and n-alkanes (Wang et al., 2016a; Xu et al., 2015). Other quantified compounds include semi-volatile organic compounds of alkanones, alkanoic acid methylesters, long chain linear alkyl benzenes (Schnelle-Kreis et al., 2007), low molecular weight carboxylic acids, amino acids, aliphatic amines (Yang et al., 2005; Khare et al., 2011), monosaccharide anhydrides (including levoglucosan), saccharides, methoxyphenols, resin acids, hopanes and cholestane (Mikuška et al., 2015), among others. In short, only a fraction of organic matter present in $PM_{2.5}$ has been identified, e.g., more than 30

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individual WSOC species accounts for only 8% of organic carbon present in PM, and less than 7% of nonpolar organic matter (46 compounds) identified (Yang et al., 2005). Recently, persistent organic pollutants (POPs) including PCDD/Fs (Cortés et al., 2014), organochlorine pesticides (Ji et al., 2015), polychlorinated biphenyl (PCB), and polybrominated diphenyl ethers (Pan et al., 2011; Nie et al., 2014; Wang et al., 2014) present in airborne PM have received considerable attention due to their potential health hazards. As for nitrosamines, only a few studies (Ramírez et al., 2012; Akyüz and Ata, 2013; Aragón et al., 2013; Farren et al., 2015) deal with $PM_{2.5}$, while most others cover occurrence, formation, and degradation of nitrosamines in aqueous environment (Krasner et al., 2013).

Typically, atmospheric $PM_{2.5}$ contains a variety of hazardous air pollutants, such as PCDD/Fs, PCBs, PAHs, and organic nitrogen compounds. Among them, *N*-nitrosamines are nitrogen-containing heterocyclic compounds that have been classified as extremely potential human carcinogens by the International Agency for Research on Cancer (IARC, 2016). Some of them, such as *N*-nitrosomethylamine (NMEA), *N*-nitrosodiethylamine (NDEA), *N*-nitrosodimethylamine (NDMA), *N*-nitrosodi-n-propylamine (NDPA), *N*-nitrosomorpholine (NMor), *N*-nitrosopyrrolidine (NPyr), *N*-nitrosopiperidine (NPip), *N*-nitorosodi-n-butylamine (NDBA), and *N*-nitrosodiphenylamine (NDPhA), can have a mutagenic effect on humans (U.S.DHHS, 2014). In particular, NDMA is a very carcinogenic chemical, so it is classified as Group 2A by IARC (IARC, 2016) and is one of more abundant nitrosamines than other nitrosamines in the atmosphere (Farren et al., 2015), in a variety of food (Park et al., 2015), source and drinking water (Wang et al., 2016b) and in rubber manufacturing industry (Spiegelhalder and Preussmann, 1983; Jönsson et al., 2009).

In air sampling from industrial setting, the average concentration of total nitrosamines in the workers' breathing zone in one large warehouse of finished rubber products was 2.7 $\mu g\ m^{-3}$ with NDMA accounting for 82% (Carrier et al., 2011). The mean levels for NDMA and NMor near 17 rubber factories are 1–10 $\mu g\ m^{-3}$ (up to 360 $\mu g\ m^{-3}$).[26] About 18% of 709 air samples from rubber vulcanization exceeded the German nitrosamine target value of 2.5 $\mu g\ m^{-3}$ with the salt bath curing process exhibiting high nitrosamine levels (Goss-Jr. et al., 2006); 90% of the 96 measurements are over the target value, with many values exceeding 20 $\mu g\ m^{-3}$ (Oury et al., 1997). In a study of Swedish rubber industry, Jönsson et al. (2009) reported that the level up to 36 $ng\ m^{-3}$ was found with workers vulcanizing with salt bats encountering the highest median 4.2 $ng\ m^{-3}$.

In addition to the primary emissions from the polymer industry, incinerators for combusting rubber and plastic materials, and automobiles, *N*-nitrosamines including NDMA can be formed through the reactions between nitrosating agent (e.g., nitrite) with amine precursors (i.e., dimethylamine) in the atmosphere (Ge et al., 2011).

In general, *N*-nitrosamines are degraded rapidly under sunlight, so their atmospheric concentrations are higher at night (Hanst et al., 1977; Tuazon et al., 1984). However, in the urban areas of Asian countries where smog and haze are not uncommon (e.g., Seoul, Beijing, etc.), solar radiation is often blocked, and more *N*-nitrosamines may accumulate even during the daytime. Therefore, the regular monitoring of *N*-nitrosamines is crucial to prevent possible exposure of the compounds to humans, especially in Asian countries.

Until now, only a few studies have been carried out to determine the *N*-nitrosamines in atmospheric PM (Monarca et al., 2001; Ramírez et al., 2012; Akyüz and Ata, 2013; Aragón et al., 2013; Farren et al., 2015). Most of the above studies focused on the development of analytical methods for *N*-nitrosamines in PM. In their studies, gas chromatograph (GC) coupled to tandem mass/mass spectrometry (MS/MS) was used (Akyüz and Ata, 2013; Aragón et al., 2013) or two dimensional gas chromatographs (GC × GC) coupled to a nitrogen chemiluminescence detector (NCD) were applied (Ramírez et al., 2012; Farren et al., 2015). Both GC-MS/MS and GC × GC-NCD techniques showed the satisfactory quantification ability for *N*-nitrosamines. Since all these studies used the pressurized liquid extraction (PLE) followed by a concentration step to blow the sample volume down to 0.5 mL to analyze lower concentrations, which might result in significant analyte loss and lower recovery efficiencies, particularly for volatile compounds. In particular, < 60% recovery was reported for NDMA (Ramírez et al., 2012; Aragón et al., 2013) possibly due to its relatively low boiling temperature/high vapor pressure comparing to other nitrosamines (Supporting Information (SI): Table SI-1). Extraction of PM samples by ultrasonication is generally and widely used in the analysis of carbonyl and inorganic compounds adsorbed onto the particles (Ortiz et al., 2006, 2009; Kim et al., 2011; Kim et al., 2013).

Direct liquid extraction (DLE) assisted by ultrasonication has been applied for extracting primary aromatic amines (Zhao and Suo, 2008) or aliphatic and aromatic nitrosamines from soils (Jurado-Sánchez et al., 2013). In the study performed by Zhao and Suo (2008), dichloromethane (DCM) was used as extracting solvent to achieve more than 90% recovery. On the other hand, methanol was used in the latter study with relatively low recovery (<50%). As of now, DLE assisted by ultrasonication has not been applied for extracting *N*-nitrosamines from atmospheric PM.

In this paper, therefore, we propose a simpler analytical method for measuring *N*-nitrosamines in atmospheric PM in which target analytes are extracted from samples by DCM assisted by ultrasonication and are subsequently quantified using GC-triple quadruple MS (TQMS) in a multiple reaction monitoring (MRM) mode. The GC-TQMS has been applied for the quantification of trace compounds in complex samples, owing to its high selectivity and sensitivity; for examples, residual drugs in drinking water and wastewater (Ternes et al., 1998), residual organochlorine/organophosphorus pesticides and PCBs in eggs (Bolaños et al., 2007), brominated flame retardants in fish (Kalachova et al., 2013), etc.

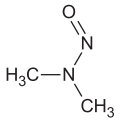
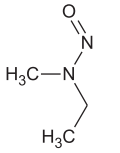
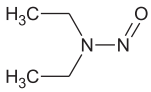
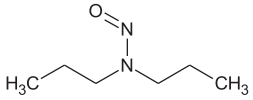
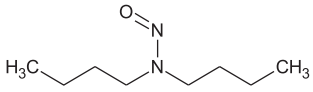
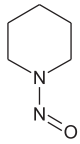
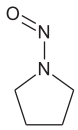
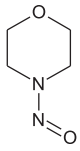
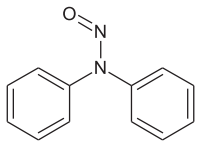
Most importantly, the developed analytical method was applied to quantify *N*-nitrosamines in PM of the air samples collected in Seoul. The developed method with a simple sample pretreatment will allow a better understanding of the trace nitrogen-containing organic compounds in atmospheric PM. To the best of our knowledge, this is the first attempt to quantify *N*-nitrosamines in airborne PM in Asia. The information obtained through future continuous and systematic monitoring along with PAHs and PCBs data should assist the regulatory agency to develop exposure risks from these carcinogenic compounds present in airborne PM.

2. Material and method

2.1. Chemicals and reagents

A mixture of a standard solution (each 2000 mg L^{-1}) of 9 *N*-nitrosamines (EPA 8270/Appendix IX Nitrosamines Mix) containing NDMA, NMEA, NDEA, NDPA, NDBA, NPip, NPyr, NMor, and NDPhA was obtained from Sigma Aldrich (Bellefonte, PA, USA). The standard solution for instrument calibration was prepared in DCM (GC grade, 99.5%), obtained from Kanto Chemical (Tokyo, Japan). Working standard solutions (200 mg L^{-1}) of 9 *N*-nitrosamines were prepared prior to use, and stored in the dark in a freezer. The chemical and physical properties, including the molecular weight, octanol-water partition coefficient (K_{OW}), organic carbon-water partition coefficient (K_{OC}), and water solubility of each compound along with their respective carcinogen classification (IARC, 2016)

Table 1
Molecular weight, K_{OW}, K_{OC}, and water solubility of the target compounds and their respective carcinogen classifications by IARC.

IARC classification (IUR)[a]	Compound (CAS number)	Acronym	Chemical formula	Structure[b]	Molecular weight (g mol^{-1})	K_{OW}[c]	K_{OC}[c]	Water solubility[c] (mg L^{-1})
Group 2A (4.6×10^{-3})	*N*-nitrosodimethylamine (62-75-9)	NDMA	$C_2H_6N_2O$		74	0.27	12	1.0×10^6
Group 2B (6.3×10^{-3})	*N*-nitroso-n-methylethylamine (10595-95-6)	NMEA	$C_3H_8N_2O$		88	1.10	4–73	3.0×10^5
Group 2A (1.0×10^{-2})	*N*-nitrosodiethylamine (55-18-5)	NDEA	$C_4H_{10}N_2O$		102	3.02	43	1.1×10^5
Group 2B (2.0×10^{-3})	*N*-nitrosodi-n-propylamine (621-64-7)	NDPA	$C_6H_{14}N_2O$		130	2.29	10.2	1.3×10^4
Group 2B (3.1×10^{-3})	*N*-nitrosodi-n-butylamine (924-16-3)	NDBA	$C_8H_{18}N_2O$		158	427	1.4×10^3[d]	1.3×10^3
Group 2B (2.7×10^{-3})	*N*-nitrosopiperidine (100-75-4)	NPip	$C_5H_{10}N_2O$		114	22.9	37[d]	7.6×10^4
Group 2B (6.0×10^{-4})	*N*-nitrosopyrrolidine (930-55-2)	NPyr	$C_4H_8N_2O$		100	0.65	19[d]	1.0×10^6
Group 2B (1.9×10^{-3})	*N*-nitrosomorpholine (59-89-2)	NMor	$C_4H_8N_2O_2$		116	0.36	17[d]	8.6×10^5
Not classified (2.6×10^{-6})	*N*-nitrosodiphenylamine (86-30-6)	NDPhA	$C_{12}H_{10}N_2O$		198	1.4×10^3	1.2×10^3	35

[a] Inhalation Unit Risk; unit: $(\mu g\ m^{-3})^{-1}$, California EPA. OEHHA Chemical Database; http://oehha.ca.gov/chemicals. Accessed on August 20, 2016.
[b] Chemical structures were drawn using MarvinSketch v.15.10.12 (ChemAxon Ltd., Budapest, Hungary).
[c] U.S.DHHS, 2014.
[d] Ohio EPA. http://epa.ohio.gov/portals/32/pdf/Chem_Phys_Tox.PDF. Accessed on August 20, 2016.

are provided in Table 1.

2.2. Direct liquid extraction (DLE)

Conventionally, the PLE method has been applied to extract *N*-nitrosamines from atmospheric particles with the extracted sample being vaporized for concentration (Ramírez et al., 2012; Akyüz and Ata, 2013; Aragón et al., 2013; Farren et al., 2015). Unfortunately, this sample extraction/concentration method often results in the loss of target analytes, as stated above. Therefore, the ultrasonication-assisted DLE method was applied to extract *N*-nitrosamines from samples, which does not require the evaporation procedure as a concentration step. DCM was chosen as the extraction solvent because it was reported as the best extracting solvent based on the recovery tests (Akyüz and Ata, 2013; Aragón et al., 2013).

Fig. 1 shows the sample pretreatment procedure for the PM samples used in this study. Briefly, a PM filter was initially weighed, then cut in two pieces and one of the two half pieces was inserted into a 20 mL vial. Subsequently, 5 mL of DCM was added to the vial

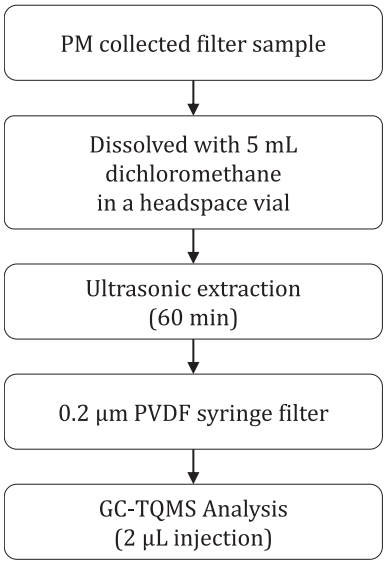


Fig. 1. Flow chart of sample extraction method used in this study.

to completely soak the filter paper. The headspace vial was sealed with a PTFE septum. The sealed vial was placed in an ultrasonic bath to extract the analytes from the PM (Fig. SI-1). Ultrasonication was operated at 40 kHz for 1 h with ice-packs to keep the temperature of the water bath below 10 °C to prevent any thermal dissociation of target analytes. Finally, the extracted samples were filtered through a 0.2 μm polyvinylidene fluoride syringe filter (Advantec, Tokyo, Japan), and injected into the GC-TQMS for quantification. By applying ultrasonic sample extraction for the sample in a sealed vial, volatilization of the analytes from the sample during the extraction process was prevented.

2.3. Chromatographic analysis

Chromatographic analysis was carried out on a GC-TQMS system (GCMS-TQ8040™, Shimadzu, Kyoto, Japan). Separation of the target analytes in the sample was achieved using a Stabilwax-MS capillary column (30 m × 0.25 mm i.d., 0.25 μm film thickness; Restek, Bellefonte, PA, USA). The oven temperature program was as follows. Initially, it was held at 60 °C for 2 min, increased to 140 °C at 8 °C min^{-1} for 8 min, then further to 240 °C at 40 °C min^{-1}, and held at the final temperature for 10 min. The helium (purity > 99.999%) was used as a carrier gas at a flow rate of 1.0 mL min^{-1}. The temperature of the injection port was 230 °C and the automatic injection of 2 μL of the samples was performed using a Shimadzu AOC-5000 autosampler (CTC Analytics, Zwinger, Switzerland). The splitless injection mode with high pressure (250 kPa) was applied. The analytes were ionized by electron-impact ionization (EI) at 70 eV. The MS ionization and interface temperatures were maintained at 200 and 240 °C, respectively. The data were acquired by using GCMSsolution™ software (Shimadzu, Kyoto, Japan). The external standard calibration method was applied to quantify the target compounds, and the unknown compounds were confirmed by the intensity ratio of the product ion peaks in MRM mode.

2.4. Method validation

To examine the validity of the proposed method, the linearity, recovery (%), method detection limit (MDL), and repeatability (% RSD, $n = 7$) were evaluated (Table 3). The MDL was determined by multiplying the Student t-value to the standard deviation (SD) calculated with 7 replicates of a standard mixture containing 9 target analytes of 0.5 ng mL^{-1} each.

For the recovery tests, 9 *N*-nitrosamines at three levels (4, 20 and 28 pg) were spiked onto the quartz fiber filters directly; they were then extracted with DCM as described above. The recovery tests for each level were carried out in triplicate. Repeatability of the developed method was evaluated by spiking a standard containing the nine target compounds (2.5 ng) onto a filter before extraction. Then, % relative standard deviation (%RSD; $n = 7$) was calculated for each analyte.

Extraction efficiency of the developed method for each of 9 *N*-nitrosamines was evaluated by extracting the extracted PM filters once more; it was then calculated by dividing the amount obtained from the first extraction by the sum of the amounts obtained from the first and second extractions.

2.5. Sample collection for application of developed method

$PM_{2.5}$ samples were collected using a cyclone sampler (URG-2000-30FG, Chapel Hill, NC, USA). For PM_{10} collection, a cyclone PM_{10} sampler mounted with a filter pack (URG-2000-30ENB, Chapel Hill, NC, USA). The samplers were operated for 24 h at 16.7 L min^{-1} for collecting $PM_{2.5}$, and PM_{10}, respectively. Quartz fiber filters with a diameter of 47 mm (Pallflex, Putnam, CT, USA) were used for both $PM_{2.5}$ and PM_{10} samplers. Once the samples were collected, they were transferred to petri slides (Millipore, Temecular, CA, USA), which were then placed in a sealed plastic bag. Finally, the bag was wrapped with aluminum foil and stored in a freezer at < −50 °C until analysis.

A total of 56 air samples were collected to measure the $PM_{2.5}$ contents at two different locations in Seoul, Korea in the fall (from October to November): 28 samples from a roadside (37°28′40" N, 126°52′53" E) and 28 from a residential area (37°36′57" N, 127°00′35" E) in Seoul, Korea; no industrial plant is located in the city. The atmospheric temperature was 7–19 °C. While only $PM_{2.5}$ samples were collected at the residential site, both $PM_{2.5}$ and PM_{10} samples were collected at the roadside.

3. Results and discussion

3.1. GC-MS/MS

Chromatographic methods using a GC-TQMS with chemical ionization (CI) and EI were used in previous studies, in which *N*-nitrosamines were quantified from the atmospheric PM samples. In these studies, a non-polar or a mid-polar column was used to quantify the *N*-nitrosamines (Akyüz and Ata, 2013; Aragón et al., 2013) which seems counter-intuitive considering their less hydrophilicity. Considering their relatively low K_{OW} and K_{OC} values and high water solubility (Table 1), a polar column should be used to obtain better separation and sharper peaks. Therefore, in the present study, a polar capillary column was applied to separate the target *N*-nitrosamines. All of the 9 *N*-nitrosamines were resolved completely with the oven temperature program described above, as shown in Fig. 2.

The MRM conditions of TQMS along with the collision energy (CE, V) were optimized for analyzing a mixture of 9 *N*-nitrosamines standards. The precursor ions of 9 compounds were obtained with EI. The CE values for each quantitative and qualitative ion were varied between 0 and 45 V to acquire the highest peak intensities for the product ion used for quantification, as well as the others used for qualification. Table 2 lists the retention time, quantitative ions (m/z), qualitative ions (m/z) and respective CE value for each of the 9 *N*-nitrosamines from the optimized MRM analytical conditions.

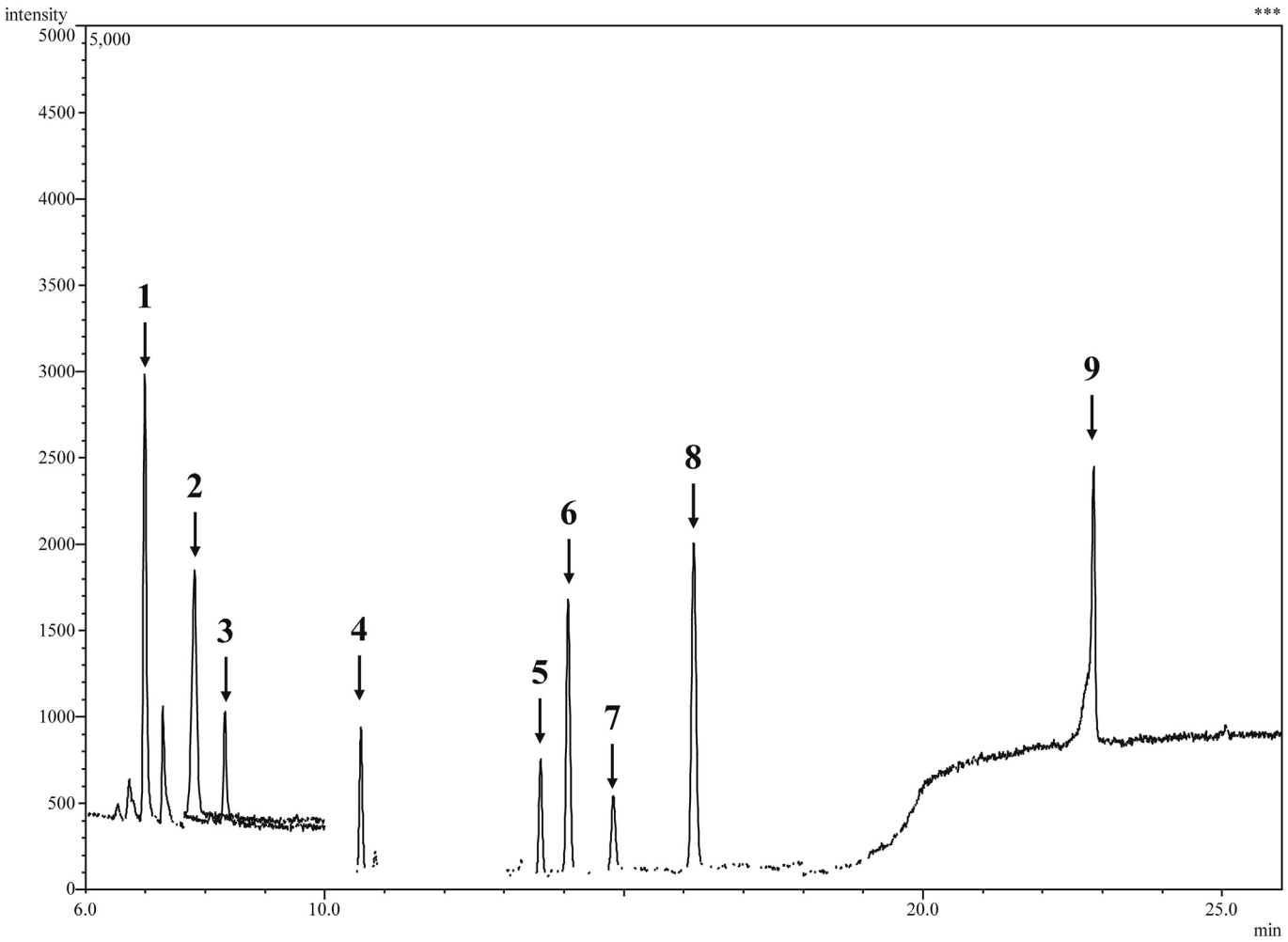


Fig. 2. Chromatogram of 9*N*-nitrosamine standards (5 ng mL^{-1}) obtained from MRM analysis using GC-TQMS. 1: NDMA, 2: NMEA, 3: NDEA, 4: NDPA, 5: NDBA, 6: NPip, 7: NPyr, 8: NMor, 9: NDPhA.

Table 2
Retention time, quantitative ions, qualitative ions and respective collision energy (CE) of the 9 *N*-nitrosamines from the optimized MRM analytical conditions.

Compound	Retention time (min)	Quantitative Ion (*m/z*)	CE (V)	Qualitative Ion (*m/z*)	CE (V)
NDMA	7.02	74 → 44	7	74 → 42	21
NMEA	7.85	88 → 71	5	88 → 57	10
NDEA	8.36	102 → 57	13	102 → 75	5
NDPA	10.69	130 → 113	5	130 → 102	5
NDBA	13.65	158 → 141	5	158 → 99	9
NPiP	14.09	114 → 84	9	114 → 55	20
NPyr	14.87	100 → 70	7	100 → 68	9
NMor	16.20	116 → 86	5	116 → 56	12
NDPhA	22.89	169 → 168	13	169 → 66	23

3.2. Direct liquid extraction (DLE)

Often DLE is applied along with subsequent sample evaporation for concentrating target analytes (Ramírez et al., 2012; Aragón et al., 2013). However, this method suffers from low recoveries for NDMA and NMEA; recovery values below 50% or even worse were reported in the literature. Based on their volatility values (i.e., 5.00 and 2.28 mm Hg for NDMA and NMEA, relatively (Table SI–1), it is expectable that some of the compounds can be lost by the evaporation step. For this reason, the DLE method assisted with the ultrasonication was applied without an evaporation step to reduce loss of analytes.

The extraction efficiencies of the proposed method were estimated with real PM_{10} and $PM_{2.5}$ samples, as listed in Table 3. Of the 9 *N*-nitrosamines, however, NDPA was rarely detected in the real samples; thus, the extraction efficiency for NDPA could not be determined. 5 mL DCM was applied to each sample used for extraction efficiency. The mean extraction efficiency estimated with real PM_{10} and $PM_{2.5}$ samples was greater than 88%.

3.3. Method validation

The proposed method consisting of the DLE in junction with ultrasonication and the subsequent GC-TQMS showed excellent performance in its validation test. Table 3 shows the result of the method validation test: the linearity, recovery, MDL, and repeatability were evaluated. The result is also compared with those from others' studies (Table SI–2).

The determined MDLs ranged from 0.03 pg for NDPA to 0.09 pg for NMEA. In the literature, a quite wide range of MDLs or LODs has been reported; from pg to sub-ng level (Akyüz and Ata, 2013; Aragón et al., 2013; Farren et al., 2015).

The recoveries of the 9 *N*-nitrosamines ranged from 92 to 117% for all the three mass levels (i.e., 4, 20, and 28 pg), as shown in Table 3, even those for NDMA and NMEA (92–106%); excellent

Table 3
Linearity, extraction efficiency, recovery, method detection limit (MDL), and repeatability of the sample filters for 9 *N*-nitrosamines.

Compound	Linearity (r^2)	Mean extraction efficiency (%, $n = 3$)		Recovery (%, $n = 3$)			MDL or LOD (pg)				Repeatability (%RSD, $n = 7$)
		PM_{10}	$PM_{2.5}$	4 pg	20 pg	28 pg	This study MDL	A	B	C	
NDMA	0.9992	95 ± 3	91 ± 7	102 ± 2	92 ± 7	106 ± 11	0.05	2.3	16.6	47.8	1.5
NMEA	0.9992	91 ± 8	93 ± 3	105 ± 3	97 ± 9	99 ± 8	0.09	2.6	15.1	478.1	2.9
NDEA	0.9994	88 ± 2	88 ± 6	109 ± 2	97 ± 2	104 ± 6	0.07	2.0	13.6	47.8	2.3
NDPA	0.9994	–	–	117 ± 8	92 ± 13	94 ± 7	0.03	3.0	10.6	35.9	0.9
NDBA	0.9997	93 ± 3	97 ± 1	114 ± 6	96 ± 9	96 ± 6	0.07	4.4	9.1	23.9	2.1
NPip	0.9996	89 ± 2	92 ± 3	113 ± 6	98 ± 11	99 ± 8	0.06	3.9	4.5	35.9	1.8
NPyr	0.9997	91 ± 4	95 ± 4	113 ± 10	97 ± 5	100 ± 6	0.07	0.6	6.8	23.9	2.2
NMor	0.9998	96 ± 3	97 ± 4	113 ± 7	96 ± 10	97 ± 6	0.04	2.4	7.6	119.5	1.4
NDPhA	0.9993	96 ± 3	89 ± 8	111 ± 15	100 ± 10	102 ± 8	0.08	3.0	3.0	35.9	2.1

A: LOD values provided; GC × GC-NCD applied; 1 mL final volume of extracted sample with 1 μL injection volume applied; Farren et al. (2015).
B: LOD values provided; GC-MS applied; sampled at 15 L min^{-1} for 24 h; 0.1 mL final volume of extracted sample with 1 μL injection volume applied; Akyüz and Ata (2013).
C: MDL values provided; GC-Ion Trap MS applied; sampled at 0.83 m^3 min^{-1}; 5 mL final volume of extracted sample with 1 μL injection volume applied; Aragón et al. (2013).

recoveries could be obtained without the additional sample evaporation procedure for analyte concentration. For comparison, recoveries of 50–70% for both NDMA and NMEA were reported when the PLE and GC/MS or LC/MS based method was applied (Aragón et al., 2013; Qian et al., 2015). On the other hand, Farren et al. (2015) could achieve recoveries of 91–92% for NDMA and NMEA by using their PLE method in which a higher extraction temperature (80 °C) was applied but the evaporation step was omitted. Using two-step liquid extraction with alkaline water and DCM followed by evaporation also showed high recovery of 97% for both NDMA and NMEA (Akyüz and Ata, 2013).

Regarding repeatability (%RSD) of the analytical method, it was calculated to be below 3% for all the target compounds, which is excellent and probably due to the exclusion of the evaporation step from the sample pretreatment procedure. For comparison, the methods based on PLE showed relatively high 7–18% repeatability (Aragón et al., 2013; Farren et al., 2015).

Based on the results obtained in this study, it is clearly demonstrated that DLE with ultrasonication assistance but without an evaporation step and the subsequent quantification using GC-TQMS can accurately and precisely analyze all the nine semi-volatile nitrosamines. In addition, we believe that this technique can be applied in other studies where other trace (semi)volatile organic compounds, as PAHs are analyzed from PM.

3.4. Application of developed method to nitrosamines in atmospheric PM

A total of 56 $PM_{2.5}$ samples were collected at two sites (i.e., a residential and a roadside site) to determine the 9 *N*-nitrosamines in the PM using the developed method. At the roadside site, both PM_{10} and $PM_{2.5}$ samples were collected, while only $PM_{2.5}$ samples were collected at the residential site. Fig. 3 shows the chromatograms of the 9 *N*-nitrosamines in PM_{10} (a) and $PM_{2.5}$ (b) obtained from the MRM analysis using GC-TQMS as an example. Seven of 28 $PM_{2.5}$ samples were collected along with PM_{10} ones from the roadside on the same days. The concentrations of PM_{10} and $PM_{2.5}$ measured at the roadside were 34–86 and 24–67 μg m^{-3}, respectively: $PM_{2.5}/PM_{10}$ of 0.63–0.78. The concentrations of $PM_{2.5}$ measured at the residential area were 16–60 μg m^{-3}, which were statistically lower than those measured at the roadside ($p < 0.01$; calculated by the Mann-Whitney test), indicating possible impact of mobile sources. The $PM_{2.5}$ levels measured in the residential area of Seoul were to some degree higher than those measured in London, UK (i.e., 5–50 μg m^{-3}) (Farren et al., 2015) and an urban area near highway in Cincinnati, US (i.e., 15 μg m^{-3}) (Grinshpun et al., 2014), but lower than residential area in Shanghai (i.e., 103 μg m^{-3}) (Wang et al., 2013).

Again, since most nitrosamines are completely water soluble and hydrophilic (e.g., K_{OW} of 0.27, K_{OC} of 12, and water solubility of 1.0 × 10^6 mg L^{-1} for NDMA (Table 1)), it is unlikely that these compounds can be adsorbed onto particles (U.S.EPA, 2014). Rather, it is expected to exist in aqueous environment. Yet, it has been demonstrated that archived biosolids contains high amounts of nitrosamines, e.g., average concentration of NDMA is 504 ng g^{-1} with NDPhA most frequently detected (0.7–147 ng g^{-1}) (Venkatesan et al., 2014); the K_{OW} are 0.27 and 1400 for NDMA and NDPhA, respectively (Table 1). The exact reason for the above phenomenon is unclear. Nonetheless, under atmospheric conditions, these nitrosamine gaseous compounds cannot be adsorbed to $PM_{2.5}$, unlike hydrophobic PAHs.

The compounds detected at both sampling sites were NDMA, NDEA, NDBA, and NMor; the majority of samples detected above 90% of the frequency. The mean concentrations of NDMA, NDEA, NDBA, and NMor for the $PM_{2.5}$ samples collected at the roadside were 0.55 ± 0.51, 0.41 ± 0.14, 0.29 ± 0.12, and 1.02 ± 1.13 ng m^{-3}, respectively (Table 4, Fig. 4a), with 2.7 ± 1.7 ng m^{-3} for the mean concentration of Σ9 *N*-nitrosamines (Fig. 4b). Those measured at the residential site were 0.30 ± 0.30, 0.31 ± 0.14, 0.22 ± 0.22, and 0.70 ± 0.85 ng m^{-3} for NDMA, NDEA, NDBA, and NMor, respectively (Table 4, Fig. 4a); the mean concentration of Σ9 *N*-nitrosamines was 2.0 ± 1.2 ng m^{-3} (Fig. 4b). Apparently, *N*-nitrosamines concentration measured at the roadside was higher than that measured at the residential site ($p < 0.05$); especially NDMA, NDEA, NDBA, NMor, and NDPhA concentrations of the roadside were higher than those of the residential site (Table 4).

Since Kneip et al. (1983) first reported the evidence of nitrosamines in airborne particles in 1983, there have been few limited studies concerning the occurrence of nitrosamines in ambient $PM_{2.5}$. Our findings along with few others clearly demonstrate the occurrence of nitrosamines in $PM_{2.5}$ even in urban, residential and rural sites. Good correlations between *N*-nitrosamines and $PM_{2.5}$ are observed in this study for the samples collected both at the roadside and at the residential area; $r = 0.89$ for the roadside samples and 0.94 for the residential ones. The good correlation clearly indicates the amount of *N*-nitrosamines is related to the $PM_{2.5}$ level in the air. The ratio between Σ9 *N*-nitrosamines and $PM_{2.5}$ in our study was calculated 0.065 ng *N*-nitrosamines μg^{-1} $PM_{2.5}$ with the decent regression coefficient, $R^2 = 0.71$; 0.082 and 0.052 ng *N*-nitrosamines μg^{-1} $PM_{2.5}$ for roadside and residential site, respectively (Fig. 4c). This value is lower than 0.19 ng (Σ8 *N*-nitrosamines) μg^{-1} $PM_{2.5}$ reported by Farren et al. (2015). The lower

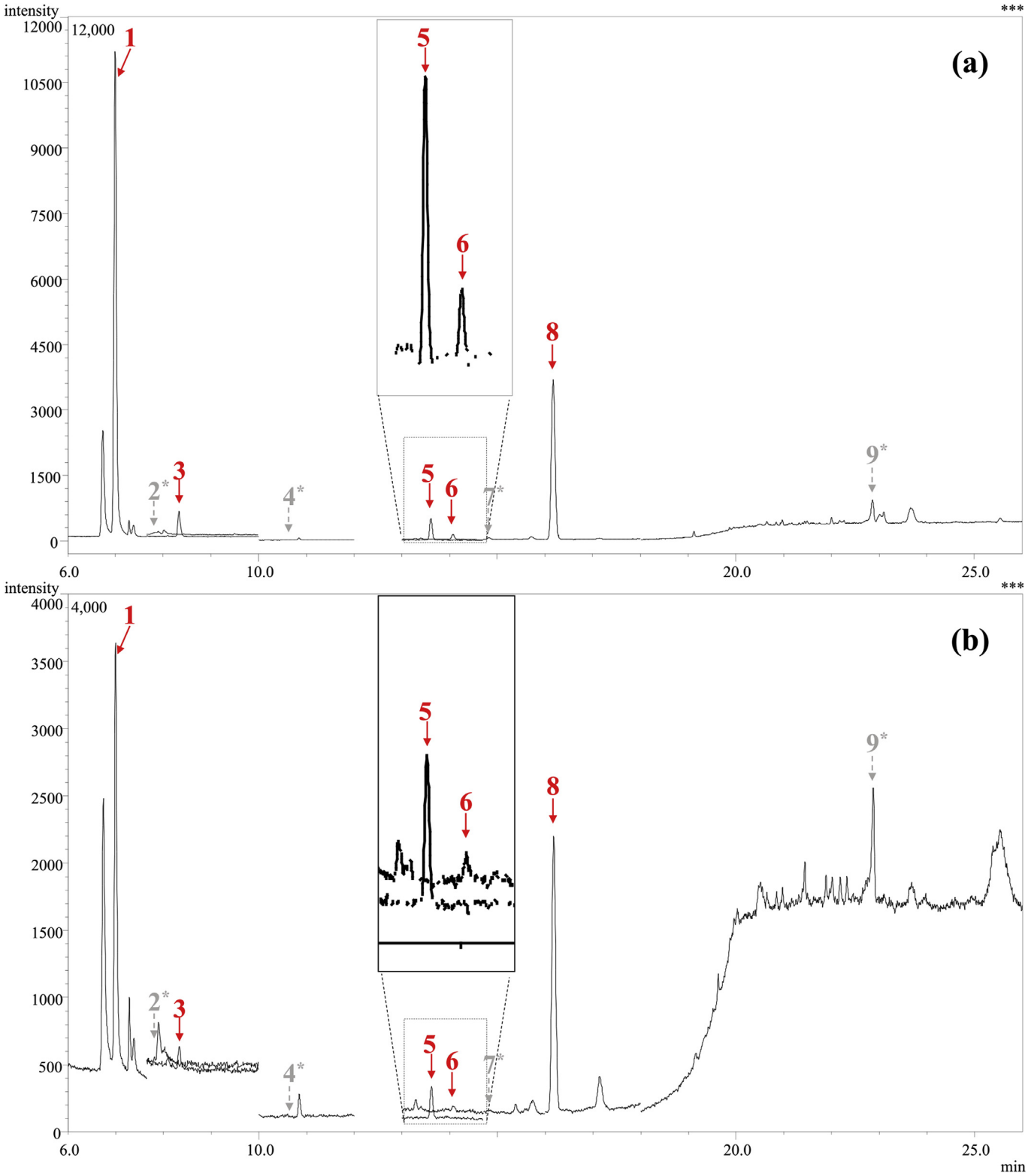


Fig. 3. Comparison of chromatograms for 9*N*-nitrosamines in PM_{10} (a) and $PM_{2.5}$ (b) collected at roadside. 1: NDMA, 2: NMEA, 3: NDEA, 4: NDPA, 5: NDBA, 6: NPip, 7: NPyr, 8: NMor, 9: NDPhA. * indicates below MDL.

ratio in our study is apparently due to much higher $PM_{2.5}$ levels.

N-nitrosamines present in $PM_{2.5}$ (2.7 ± 1.7 ng m^{-3} for the roadside, and 2.0 ± 1.2 for the residential site) observed in this study (Fig. 4b) are comparable with those reported by others (Farren et al., 2015), except for those measured at the site near coal mining and steel industry (10.6 ± 13.1 ng m^{-3} in Summer and 84.0 ± 36.6 ng m^{-3} in Winter) (Akyüz and Ata, 2013) (Fig. 4b). Noticeably, these values are several orders of magnitude higher

Table 4
9 *N*-nitrosamines concentrations in PM_{10} and $PM_{2.5}$ collected at roadside, and residential area.

Compound	Roadside								Residential area			
	PM_{10} (ng m^{-3}, $n = 7$)				$PM_{2.5}$ (ng m^{-3}, $n = 28$)				$PM_{2.5}$ (ng m^{-3}, $n = 28$)			
	Mean	Geometric Mean	Median	Frequency (%)	Mean	Geometric Mean	Median	Frequency (%)	Mean	Geometric Mean	Median	Frequency (%)
NDMA	3.45	3.39	3.54	100	0.55	0.38	0.41	100	0.30	0.21	0.18	100
NMEA	0.01	0.01	0.01	29	0.01	0.01	0.01	32	0.01	0.01	0.01	10
NDEA	0.85	0.80	0.71	100	0.41	0.39	0.41	100	0.31	0.28	0.28	100
NDPA	0.01	0.01	0.01	14	0.01	0.01	0.01	21	0.01	0.01	0.01	14
NDBA	0.60	0.55	0.44	100	0.29	0.27	0.29	100	0.22	0.17	0.15	100
NPip	0.07	0.06	0.07	71	0.04	0.03	0.03	100	0.04	0.04	0.04	83
NPyr	0.53	0.52	0.51	57	0.30	0.29	0.31	86	0.43	0.42	0.42	90
NMor	1.31	1.23	1.30	100	1.02	0.66	0.65	100	0.70	0.41	0.40	93
NDPhA	0.01	0.01	0.01	57	0.18	0.16	0.16	86	0.07	0.07	0.06	93
Σ9 Nitrosamines (ng m^{-3})	6.5	6.3	6.1	–	2.7	2.4	2.8		2.0	1.7	1.6	–

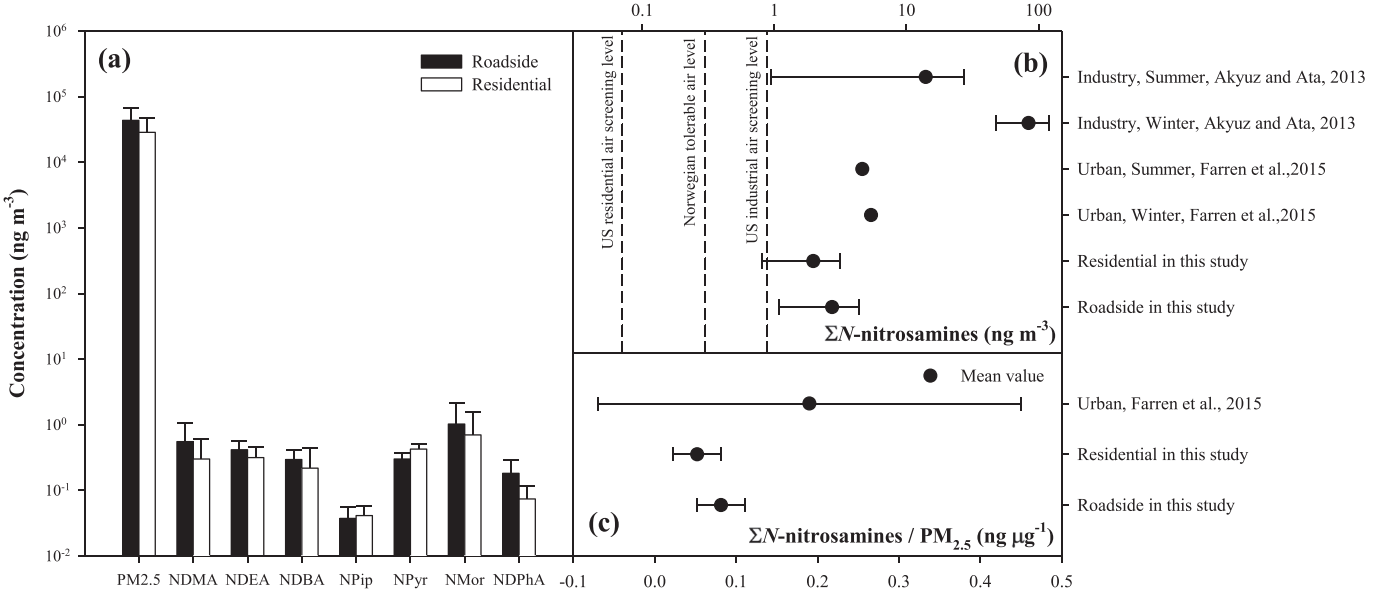


Fig. 4. Concentrations of 9*N*-nitrosamines measured at roadside and residential sites (a), and comparisons of *N*-nitrosamine concentrations in $PM_{2.5}$ measured from different studies (b) and of *N*-nitrosamines/$PM_{2.5}$ ratios (c).

than Norwegian tolerable air concentration (0.3 ng m^{-3}) (Låg et al., 2011) and US residential air screening level of 0.07 ng m^{-3} and an industrial air screening level of 0.88 ng m^{-3} based on target cancer risk of 10^{-6} (U.S.EPA, 2016).

Although it is unclear as the reason for such high levels in our residential area, the finding of nitrosamines even in rural sites has been previously reported, e.g., 3 ng m^{-3} (in $PM_{2.5}$) in rural forested area in New York (Kneip et al., 1983) and up to 497 ng L^{-1} in fog samples collected from a rural site in Central Pennsylvania (Straub et al., 2012). The regional/long range transport of $PM_{2.5}$ has long been recognized (Kaneyasu et al., 2014) and this may explain the presence of nitrosamines in $PM_{2.5}$ in remote areas. However, the extent of transport of nitrosamines from other polluted areas remains to be investigated.

3.5. Fate of nitrosamines in atmosphere

Since there is no industrial plant in the city, the observation of the atmospheric *N*-nitrosamines in this study has been attributed to direct emission of the compounds by motor vehicles or the oxidation of secondary amines present in the air or emitted from vehicle exhausts (Goff et al., 1980; Ge et al., 2011; Kang et al., 2016). Considering the extremely short life time for nitrosamines in the air, the presence of nitrosamines in $PM_{2.5}$ may not solely come from the direct emission of these compounds. The life time for nitrosamines is in the order of minutes, e.g., photolysis of 5–30 min for NDMA and NMor (Hanst et al., 1977; Larsen, 2011); life time increases in winter season and nighttime due to much lower photoenergy. Therefore, the formation of these atmospheric nitrosamines certainly results from in situ generation from precursor gas amines (including trimethylamine, methylamine, triethylamine, diethylamine, ethylamine, and monoethanolamine) and nitrosating agent (e.g., nitrite) as well documented before (Pitts et al., 1978; Murphy et al., 2007). The presence of nitrosamines in other matrices follows the same formation route as in atmosphere, e.g., nitrosamines are formed when nitrites (as preserve or from nitrates) react with a secondary or tertiary amine (in protein) in food (U.S.DHHS, 2014); in malting and brewing process in the presence of dimethylamine, *N*,*N*-dimethyltyramine and NOx (Wainright, 1986); diesel engine emission where both amines and NOx are emitted (Ge et al., 2011); secondary amines formed during rubber curing (vulcanization) process react with nitrate/nitrite in the salt baths and NOx in air (Jönsson et al., 2009); and nicotine (a tertiary amine) induced nitrosamines since NO_2 is present in saliva and NOx

present in tobacco smoke (Hecht and Hoffmann, 1988). The fact of in situ generation of nitrosamines explains the concentration level ranging from 0.2 μg m^{-3} to 36 μg m^{-3} observed in ambient air; all sites are associated with the presence of precursor compounds (Fine et al., 1976; Rounbehler et al., 1980; Environment Canada, 1999).

In summary, the presence of nitrosamines in $PM_{2.5}$ in this study might be due to the following steps: (1) the initial formation of gaseous nitrosamines in atmosphere, (2) conversion of the gaseous compounds to aerosol phase, and (3) eventually aerosol growth via nucleation and accumulation stages (from few nanometers to hundreds of nanometers) that ends up in $PM_{2.5}$. The process is similar to the formation of secondary inorganic $PM_{2.5}$ (sulfate, nitrate and ammonia) and other secondary organic aerosols (SOA), e.g., C_2-C_6 dicarboxylic acids (Chen et al., 2007). The fact that nitrosamines have been detected in cloud and fogs (Hutchings et al., 2010) at substantial level of 8–500 ng L^{-1} even at the rural site (up to 497 ng L^{-1}) (Straub et al., 2012) clearly indicates its equilibrium between gaseous and aqueous phases. Based on thermodynamic equilibrium, Hutchings et al. (2010) in fact determined that a small gas phase concentration (<2 ng m^{-3}) translates into fog concentrations about 150 ng L^{-1}.

In fact, the formation of SOA is not just due to atmospheric reaction of volatile organic carbons (VOCs), but it also comes from other organic compounds, e.g., 30% SOA can be generated from emitted intermediate VOCs (Zhao et al., 2014). In our case, the precursor compounds may be semi-volatile and the resultant low-volatility nitrosamines as part of polycyclic organic matter are associated with $PM_{2.5}$. To the best of our knowledge, this is the first report mentioning nitrosamines as SOA in $PM_{2.5}$. The results of the present study certainly fill the knowledge gap in so many unidentified compounds in SOA. Incidentally, the average ratio of Σ9 *N*-nitrosamines/$PM_{2.5}$ is about 0.065 ng μg^{-1}; only an insignificant fraction of SOA in $PM_{2.5}$ (e.g., typically SOA/$PM_{2.5}$ ratio ranging from 0.2 to 0.5) (Mancilla et al., 2015).

Contradictory to conventional wisdom in that NDMA is not persistent in air environment due to its short half-life (Hanst et al., 1977; Environment Canada, 1999), the recent persistent observation of NDMA in $PM_{2.5}$ samples indicates otherwise. It may due to continuous renewal through in situ generation of the photolyzed nitrosamines (competition between its generation and removal) and relatively fast time for nucleation and growth stage for vapor nitrosamines converting to SOA. One other note needs to be pointed out in that the fate of nitrosamines in air includes wet and dry deposit, as also mentioned by Larsen (2011), in addition to rapid photolysis and presence as SOA in $PM_{2.5}$. This is analogous to the effect of atmospheric nitrogen deposition on the surface water quality, e.g., it accounts for 20–80% of total nitrogen load entering the Chesapeake Bay watershed (Sheeder et al., 2002). In fact, Kneip et al. (1983) have mentioned that there may be a connection between direct deposit of nitrosamines-containing PM and related pollutant in soil. Furthermore, amines have been demonstrated to exhibit deposition of the gas by wet or dry deposition of particles (Ge et al., 2011) in addition to their presence in $PM_{2.5}$ (Khare et al., 2011). Thus, the extent of impact by air deposition on the observed nitrosamines levels in surface water (up to 740 ng L^{-1}) (Kim et al., 2014) remains to be seen.

3.6. Health risk associated with nitrosamines in PM

Currently, there is no regulation as to the permissible level of nitrosamines in ambient air, although in Germany, a guideline of 1 μg m^{-3} (measured as an 8-h weighted average) for occupational exposure to nitrosamines has been established for general industry (Låg et al., 2009) and 0.5 μg m^{-3} for vulcanization in the tire industry (Jönsson et al., 2009). For comparison, extremely low air NDMA concentrations of 0.0007 μg m^{-3} and 0.0031 μg m^{-3}, respectively from WHO and US EPA, were determined based on 10^{-5} cancer risk (Låg et al., 2011).

High nitrosamine levels in PMs (i.e., 6.5 ng m^{-3} in the roadside) can bring about additional health hazards associated with these nitrosamines. Previous studies also have discussed potential health risk associated with nitrosamines in PM. For example, Akyüz and Ata (2013) indicated that the relatively high nitrosamine concentrations (winter average 84 ng m^{-3} in $PM_{2.5}$) might pose a significant cancer risk in winter for the local population near their sampling sites. Kneip et al. (1983) reported 140 pmole m^{-3} (11 ng m^{-3} based on average molecular weight of 80) in $PM_{2.5}$ in New York City. Based on average PAH level (1.35 ng m^{-3}), they stated that these nitrosamines would be more hazardous than benzo[α]pyrene (most toxic among PAHs). Farren et al. (2015) determined the lifetime cancer risk from nitrosamines in London urban $PM_{2.5}$ which exceeded the US EPA guideline (one excess cancer case per 1 million population exposed after 1 h of exposure to observed concentrations per day over the duration of an adult lifetime). In different rubber industries, Monarca et al. (2001) found NDMA (0.1–0.98 μg m^{-3}) and NMor (0.77–2.40 μg m^{-3}) in air and some extracts from $PM_{0.5}$ exhibited mutagenic with the Ames test and genotoxic with the Comet assay. It is noted, in their study, carcinogenic PAHs are also found in air samples (total 8 PAHs from 23 to 66 ng m^{-3}), but the effect of these PAHs on their mutagenic and genotoxic results should be minimal due to their much lower concentration. Jönsson et al. (2009) also found that compared to the unexposed subjects, the rubber workers had an increased risk of nosebleeds, eye and throat symptoms, hoarseness, cough, nausea, headache, and changed levels of eosinophils.

Consequently, a systematic monitoring of nitrosamines present in both ambient air and $PM_{2.5}$ including seasonal and diurnal variations of selected sites (including potential precursor sources) in the future should highlight the potential health hazards associated with the compounds.

4. Conclusions

An ultrasonication-assisted DLE followed by the quantification using a GC-TQMS system was developed to analyze *N*-nitrosamines in atmospheric PM. Unlike other commonly used methods, the sample evaporation step for analyte concentration was eliminated in the current study but excellent recoveries and reproducibilities (see the difference between reproducibility and repeatability) of 92–117% and <3%, respectively could be achieved for all the *N*-nitrosamines determined under study. The MDLs of the proposed method for the nine nitrosoamines were 0.04–0.09 pg. Considering its relative easiness and requirement of less solvent, it can be applied for a monitoring program for *N*-nitrosamines in the atmosphere. In addition, the proposed method can be used to analyze other trace amounts of (semi)volatile compounds along with the nitrosamines in PM.

Using the developed method, *N*-nitrosamines in $PM_{2.5}$ collected at a roadside and a residential site in Seoul, Korea were quantified. In short, NDMA, NDEA, NDBA, and NMor were found in $PM_{2.5}$ samples collected at both sites; the mean concentrations ($n = 28$) of NDMA, NDEA, NDBA, and NMor measured at the roadside were 0.55 ± 0.51, 0.41 ± 0.14, 0.29 ± 0.12, and 1.02 ± 1.13 ng m^{-3}, respectively.

The total *N*-nitrosamines monitored at the roadside were 1.1–9.4 ng m^{-3} which is 4–31 times higher than the guideline (i.e., 0.3 ng m^{-3}) recommended by the Norwegian Institute of Public Health (Låg et al., 2011). In addition, the US EPA has calculated a residential air screening level of 0.07 ng m^{-3} and an industrial air

screening level of 0.88 ng m^{-3} based on target cancer risk of 10^{-6} (U.S.EPA, 2016).

Lastly, it should be pointed out that the fate of degradation byproducts of atmospheric nitrosamines is *still* unknown. The degradation products include peroxyacyl nitrates, amides and nitramines (Larsen, 2011) as well as dimethylnitramine, acetamides and aldehydes (Grosjean and Parmar, 1991). Some of them are persistent (Larsen, 2011) and are also toxic (Grosjean and Parmar, 1991; Låg et al., 2009). The monitoring of these compounds in ambient air is worth of further investigation. Therefore, a more systematic monitoring program should be made for *N*-nitrosamines in PM and their degradation products in the air for the sake of the public health.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.envpol.2017.04.017.

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