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Determination of N-nitrosamines and nicotine in air particulate matter samples by pressurised liquid extraction and gas chromatography-ion trap tandem mass spectrometry

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ABSTRACT

N-nitrosamines are potentially hazardous pollutants, classified as probable carcinogenic and mutagenic by the U.S. Environmental Protection Agency (EPA). In this paper, the presence of these pollutants was studied in air samples taken at different locations of Tarragona (urban and harbour). As a result, a reliable method has been developed for determining N-nitrosamines and nicotine based on pressurised liquid extraction (PLE) and gas chromatography-(chemical ionisation) ion trap tandem mass spectrometry (GC-(CI)MS/MS). The chromatographic analysis enables the determination of these compounds in less than 13 min with total separation and good resolution between the compounds. Recovery values were higher than 80% for most of the compounds and the repeatability of the method was under 18% (5 ng m^{-3}, %RSD, $n=4$). MDLs were between 0.1 ng m^{-3} (NMor and NPip) and 2 ng m^{-3} (NMEA). NMor, NPyr, NPip and nicotine were the most frequent compounds in urban and harbour samples at concentration levels between 0.3 ng m^{-3} (NPyr) and 12.5 ng m^{-3} (nicotine) and between 0.13 ng m^{-3} (NPyr) and 3.8 ng m^{-3} (nicotine), respectively.

1. Introduction

N-nitrosamines are an important group of organic volatile contaminants which are considered to be human carcinogens [1]. These compounds are formed by nitrosation or oxidation reactions of amine precursors [2]. N-nitrosamines can also be found in other matrices such as food and alcoholic drink products [3,4], cosmetic products [5,6], chlorinated swimming pools [7,8] house dust [9–11], tobacco smoke [9,12–14], latex products [15] and others. Some studies have shown that these compounds may also be present in water [16–18] and wastewater treatment systems [19,20] due to chlorine-based disinfection processes, making them a significant group of potentially hazardous disinfection by-products [2,21].

The United States Environmental Protection Agency (US EPA) has classified N-nitrosamines in the B2 group as probable carcinogenic compounds for human health [22]. Moreover, some of these N-nitrosamines, such as N-nitrosomethylamin (NMEA), N-nitrosodiethylamine (NDEA), N-nitrosodimethylamine (NDMA), N-nitrosodi-n-propylamine (NDPA), N-nitrosomorpholine (NMor), N-nitrosopyrrolidine (NPyr), N-nitrosopiperidine (NPip), N-nitrosodi-n-butylamine (NDBA) and N-nitrosodiphenylamine (NDPhA), can have mutagenic effects on humans [22,23]. Therefore, a maximum admissible concentration level of NDMA, NDEA and NMEA in drinking water is imposed and regulated by the US EPA, due to the potentially carcinogenic effects of these compounds [1,7]. Under the restrictions, the maximum admissible concentration for NDEA, NDMA, NDBA, NPyr and NDPhA is 20, 70, 600, 2,000 and 700,000 ng/L, respectively, with a risk estimate of 10^{-4} (Unit Risk Estimate) [1,24]. Several N-nitrosamines have been found in water samples from wastewater plants at levels of 1 or 2 orders of magnitude higher than their permitted cancer risk levels [25,26]. As a result, the interest in these kinds of compounds has increased significantly.

Different chromatographic techniques have been applied to determine N-nitrosamines and nicotine. The most common technique is gas chromatography coupled to either mass spectrometry [19] or tandem mass spectrometry [2,16] with electron impact ionisation or positive chemical ionisation. Due to the low mass of these compounds, hard ionisation source (EI) gives low sensitivity and selectivity by tandem mass spectrometry (MS/MS). For this reason, using a soft ionisation source such as chemical ionisation (CI) is recommended [26]. Moreover, gas chromatography coupled to nitrogen–phosphorous [27] or nitrogen chemiluminescence detectors [9] have frequently been used. Recently, comprehensive gas chromatography (GC × GC) coupled to nitrogen chemiluminescence detector [9] and ultra-high performance liquid chromatography coupled to tandem mass spectrometry (UHPLC-MS/MS) [17] have also been applied.

Due to the low concentration levels expected for these kinds of emerging pollutants in the environment, the determination of

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N-nitrosamines and nicotine requires the use of exhaustive extraction techniques. Pozzi et al. [16], Ripollés et al. [28] and Yoon et al. [19] determined some N-nitrosamines in liquid samples (drinking water and wastewater) using solid phase extraction (SPE) as preconcentration technique. However, Llop et al. [2] determined these organic pollutants in environmental waters using headspace solid-phase microextraction (HS-SPME) as extraction/preconcentration technique. Nevertheless, when solid samples such as sludge, house dust among others were analysed, pressurised liquid extraction was applied using water [20] or organic solvents [9]. Only a few studies about the occurrence of N-nitrosamines in air samples have previously been published. These studies focus on nicotine and its derivates in different locations, such as workplaces [29], restaurants [30] and so on. However, studies about the presence of these pollutants in air particulate matter were not found in the literature. Based on previous studies [31,32] in which other emerging organic pollutants were determined in particulate matter, pressurised liquid extraction was selected for the extraction of N-nitrosamines from this kind of matrix.

For this reason, the aim of this study is to develop a reliable method based on pressurised liquid extraction (PLE) followed by gas chromatography-(chemical ionisation) ion trap tandem mass spectrometry (PLE-GC-(CI)MS/MS) for determining the presence of this group of N-nitrosamines and nicotine in air particulate matter samples from urban and harbour environments.

2. Experimental

2.1. Standards and solutions

A mixed standard solution (2,000 mg L^{-1} in methanol) of 9 nitrosamines (EPA 8270/Appendix IX) Nitrosamines Mix, from Sigma-Aldrich, (Steinheim, Germany) containing N-nitrosodimethylamine (NDMA), N-nitrosomethylamine (NMEA), N-nitrosodiethylamine (NDEA), N-nitrosodi-n-propylamine (NDPA), N-nitrosomorpholine (NMor), N-nitrosopyrrolidine (NPyr), N-nitrosopiperidine (NPip), N-nitrosodi-n-butylamine (NDBA), N-nitrosodiphenylamine (NDPhA) and an individual standard of nicotine (Sigma-Aldrich) were used. All of the reagents had a level of purity >97%. Working standard solutions of N-nitrosamines and nicotine of 100 mg L^{-1} were prepared freshly in methanol (GC grade with >99% purity) from Prolabo (VWR, Llinars del Vallès, Spain) and stored in darkness in the freezer. The structures of target compounds are shown in Table 1.

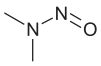
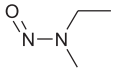
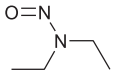
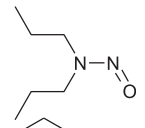
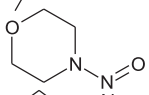
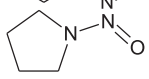
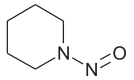
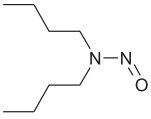
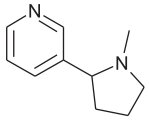
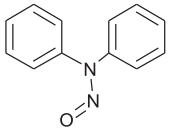
The other solvents used in the method optimization (acetone, dichloromethane and ethyl acetate) were also purchased from VWR. Hyflo Super Cel diatomaceous earth purchased from Sigma-Aldrich was used to fill the extraction cells. Helium gas with 99.999% purity (Carburos Metálicos, Barcelona, Spain) was used for chromatographic analysis.

2.2. Sampling

The aim of this study is to investigate the presence of N-nitrosamines and nicotine in air samples from Tarragona's harbour area. Tarragona harbour is an important place to study because of the high impact of daily shipping activity that involves the emission of different kinds of particulate materials, leading to continuous pollution due to road transport and ship exhaust. Moreover, samples from city centre were also analysed in order to compare the presence of these pollutants in two locations of Tarragona.

A total number of 18 samples (12 from the harbour and six from the city centre) were collected using a TE-6070 PM_{10} High Volume Air Sampler (Tisch Environmental, Inc., Cleves, Ohio, USA).

Table 1
Chemical structures and molecular weight (g/mol) of target N-Nitrosamines and nicotine.

Compound	Molecular structure	Molecular weight (g/mol)	Boiling point (°C)
N-nitrosodimethylamine (NDMA)		74.08	152
N-nitrosomethylethylamine (NMEA)		88.11	163
N-nitrosodiethylamine (NDEA)		102.14	176
N-nitrosodi-n-propylamine (NDPA)		130.19	206
N-nitrosomorpholine (NMor)		116.12	224
N-nitrosopyrrolidine (NPyr)		100.12	214
N-nitrosopiperidine (NPip)		114.15	219
N-nitrosodi-n-butylamine (NDBA)		158.24	116
Nicotine		162.23	244
N-nitrosodiphenylamine (NDPhA)		198.22	364

The samples were taken after a period of 24 h at a flow rate of *ca.* 0.83 m^3 min^{-1} on PM10 micro-fibre quartz filters (media 8 in. × 10 in.) supplied by Whatman (Maidstone, UK). The samples taken with QFF filters were wrapped in aluminium foil, protected with a sealable plastic bag and kept in the freezer until analysis.

2.3. Pressurised liquid extraction

An Accelerated Solvent Extraction system (ASE 200 from Dionex, Sunnyvale, CA, USA) was used to extract the compounds studied in air particulate matter samples.

A PM_{10} quarter part filter was placed in an 11 mL stainless steel extraction cell filled with a cellulose filter followed by 1 g of diatomaceous earth to prevent system block. Pressurised liquid extraction was done with ethyl acetate as the extraction solvent, at 40 °C for 5 min with the cells pressurised at 1,500 psi for one cycle. The flush volume was 60% and the purge time was 120 s. The extracts were evaporated to a final volume of 5 mL using a rotary evaporator.

For the recovery experiments and optimisation the extraction procedure, one quarter of the filters was spiked with all of the compounds before the extraction and one quarter of the filters was also used for analysing the samples.

2.4. Chromatographic analysis

The chromatographic analysis was performed on a Varian 3800 gas chromatography (GC) (Varian, Walnut Creek, CA, USA) connected to a Varian 4000 ion trap mass detector. The GC was equipped with a 1079 programmable vaporising temperature injector. The inlet was set at 200 °C and automatic injections of 1 μL of extracts were performed with a CombiPal autosampler (CTC Analytics, Zwinger, Switzerland). The column used was a Zebron ZB-50 (50%-phenyl–50%-dimethylpolysiloxane, 30.0 m × 0.25 mm × 0.25 μm), supplied by Phenomenex (Torrance, California, USA). The oven temperature programme began at 40 °C and it was increased to 100 °C at 15 °C min^{-1}, and then to 250 °C at 20 °C min^{-1} and kept at that temperature for 5 min. The helium carrier gas flow was set at 1 mL min^{-1}, at a purity of 99.999%, supplied by Carburos Metálicos (Barcelona, Spain). A filament-multiplier delay of 3 min was established in order to prevent instrument damage. The analytes were ionised by positive chemical ionisation using methanol (GC grade with >99% purity, SDS, Pepyn, France). The CI-MS-MS process was carried out by collision-induced dissociation (CID) using the resonant waveform mode. Experimental conditions are shown in Table 2.

3. Results and discussion

3.1. Gas chromatography-tandem mass spectrometry

The chromatographic method was adapted from a previous paper [2] in which N-nitrosamines were determined in environmental waters by GC-(CI)MS/MS. Because of the polarity of these compounds, the column used was the ZB-50 instead of the ZB-5 used in the above mentioned paper. Using a ZB-50 column, the compounds NPyr, NDPA and NMor were completely resolved with the oven temperature programme optimised. Under optimised conditions, the time analysis was less than 13 min.

Mass spectrometry conditions were optimised by injecting a mixed solution of N-nitrosamines and nicotine in the GC–MS/MS system. The parent ions of each compound were obtained with positive chemical ionisation, using methanol as the reagent gas. These ions correspond to $[M+H]^+$ for most of the compounds.

The CID voltage was optimised between 0 and 1 V to obtain the highest peak intensity of the product ion used for quantification, as well as of the other used for confirmation. All of the optimised parameters are shown in Table 2.

3.2. PLE optimisation

To obtain low detection limits, the volume of the extracts obtained in PLE (~20 mL) had to be reduced by evaporation. In preliminaries experiments, it was observed that some N-nitrosamines were lost during this evaporation process, especially NDMA and NMEA due to their low vapour pressure. This fact resulted in lower recovery values for these two N-nitrosamines than in the case of the others. For this reason, it is highly recommended not to evaporate the extract to dryness and to optimise the final volume of the extract. Therefore, *ca.* 20 mL of ethyl acetate spiked at 0.5 mg L^{-1} was evaporated up to 1, 2 and 5 mL to find the lower volume without compound losses. The final volumes of 1 and 2 mL gave lower recoveries and repeatability (RSD > 20%) than 5 mL (RSD < 10%) and then, 5 mL was selected as the final volume.

Before optimising the extraction procedure, initial PLE conditions were fixed, based on previous studies in which N-nitrosamines were determined in house dust [12] and sludge samples [20]. These initial conditions were as follows: extraction temperature: 60 °C; extraction time: 10 min; number of cycles: 1; flush volume: 60% and purge time: 120 s. Ethyl acetate, dichloromethane, methanol and acetone were tested as solvents for the extraction of N-nitrosamines.

To optimise the extraction solvent, a quarter of the blank filters was extracted with each solvent in order to determine the presence of these compounds. The experiments showed that these compounds were not present in blank filters. Subsequently, a quarter of the blank filters was spiked at 50 ng m^{-3} and then extraction took place with each solvent, under the above mentioned conditions. The results (Table 3) showed that the recoveries obtained when acetone, dichloromethane or ethyl acetate were used usually up to 90%, except for NDMA and NMEA. In contrast, when methanol was used as the extraction solvent the recovery values were about 50% lower than when others solvents were used, except for nicotine (97%).

Then, ethyl acetate was chosen as the extraction solvent because it displayed slightly higher repeatability for all of the compounds compared to the other solvents (Table 3). Moreover, the selected solvent is in line with previous studies [9] in which ethyl acetate was the optimum solvent to extract these compounds from house dust.

To find the optimal extraction temperature 40, 60, 80 and 100 °C were studied. The recovery values were slightly higher when 40 °C was applied, almost reaching 100%, as for example NDEA whose recovery increased from 85% (60 °C) to 95% (40 °C). In the case of NDMA and NMEA, their recoveries keep close to 65%. For this reason, 40 °C was chosen as the extraction temperature. At 80 °C and 100 °C the recovery values were similar or lower than those obtained at 60 °C (between 5 and 10% less).

The next parameter optimised was the extraction time. The extraction was tested at 5, 10 and 15 min. The recovery values when 5 or 10 min were applied were similar, from 65% (NDMA) to 118% (NDBA) and from 69% (NDMA) to 114% (NDBA), respectively. The results obtained when 15 min were applied were slightly

Table 2
Retention time (t_R), parent ions (m/z), CID amplitude (V), CID storage level (m/z), product ions (m/z) and m/z range of N-nitrosamines and nicotine.

Compound	Retention time ($_{min}$)	Parent ion (m/z)	CID Amplitude (V)	CID storage level (m/z)	Product ions (m/z)		m/z range
					Quantifier	Qualifier	
NDMA	5.19	75.0	0.56	33.0	47	44	43–85
NMEA	6.10	89.0	0.80	39.2	61	71	49–99
NDEA	6.76	103.1	0.60	45.4	75	85	55–113
NDPA	8.25	131.0	0.90	57.7	89	113	67–141
NMor	9.05	117.1	0.63	44.5	86	87	54–127
NPyr	9.07	101.1	0.70	44.5	55	70	54–111
NPip	9.23	115.1	0.63	44.5	69	70	54–125
NDBA	9.63	159.1	0.80	70.0	103	141	80–169
Nicotine	10.56	177.0	0.74	71.8	106	132	82–173
NDPhA	12.71	170.0	0.90	74.9	92	168	85–180

lower than in the cases of 5 or 10 min. Thus, to reduce time consumption, 5 min was chosen as the extraction time.

Due to the good recovery values obtained with the previous experiments in just one cycle, a single extraction cycle was selected for following experiments.

The optimal PLE parameters were applied to a sample filter to evaluate the recovery values in real samples. To calculate the recoveries obtained (Table 4), two filters were divided into four parts each. Two parts of each replicated filter were used to determine the concentration levels in the samples and the others parts were spiked at 5 and 50 ng m^{-3}. The recovery values were from 49% (NMEA) to 102% (NDBA) at 5 ng m^{-3} and 56% (NMEA) to 107% (NDBA) at 50 ng m^{-3}. These recovery values were slightly lower than the recoveries obtained when a blank filter was used, due to the matrix components. In non-spiked parts of the filters only NPyr appeared and the area was subtracted to calculate its recovery.

3.3. Method validation

The method developed to determine nine N-nitrosamines and nicotine in air particulate matter samples was validated studying the linear ranges, LODs, LOQs and the repeatability (expressed as relative standard deviation) for all the compounds, under optimised PLE conditions. The validation parameters are shown in Table 4. The linear range of the method was calculated by analysing spiked filters at concentration levels between MQL and 200 ng m^{-3} for all of the N-nitrosamines. All of the compounds showed good determination coefficients ($R^2 > 0.999$).

Table 3
PLE recoveries (%) for each N-nitrosamine and nicotine with different extraction solvents.

Compound	DCM[a]	Ethyl acetate[b]	Methanol[c]	Acetone[d]
NDMA	95	71	49	80
NMEA	70	65	36	69
NDEA	104	85	52	94
NDPA	88	98	45	92
NMor	102	115	56	111
NPyr	104	112	60	112
NPip	100	105	59	107
NDBA	89	111	40	93
Nicotine	105	91	97	118
NDPhA	85	105	58	92

The filters were spiked at 50 ng m^{-3}.

[a] %RSD, ($n=4$) < 20%.
[b] %RSD, ($n=4$) < 10%.
[c] %RSD, ($n=4$) < 30%.
[d] %RSD, (n=4) < 15%.

MDLs were between 0.1 ng m^{-3} and 2 ng m^{-3}, defined as the concentration of the analytes with a peak signal-to-noise ratio higher than three. MQLs, defined as the lowest point of the calibration curve were between 0.2 ng m^{-3} and 5 ng m^{-3}.

The repeatability of the method was calculated at two concentration levels (5 and 50 ng m^{-3}) analysing four spiked replicates for each concentration level. The results obtained were expressed as the relative standard deviation (%). The repeatability of the method ($n=4$) was less than 8% at the higher concentration level and less than 12% at the lower concentration level, except in the case of NDMA (RSD=18%), because this concentration level corresponds to its MQL.

3.4. Application of air particulate matter samples

The method developed was applied for determining nine N-nitrosamines and nicotine in air particulate matter samples from harbour and Tarragona city centre.

The most frequently compounds found at both sampling locations were NMor, NPyr, NPip and nicotine. NDMA, NMEA, NDPA, NDBA and NDPhA were not found in any sample. Table 5 shows the maximum and minimum concentration values and the frequency that each compound was identified at both sampling locations.

The most abundant compound found was nicotine at both locations. However, the concentration of this compound at Tarragona city centre was higher than at the harbour.

Moreover, this compound was found in all samples analysed in the city centre which was not the case with the harbour samples. Extracted ion chromatograms for each compound taken from a harbour sample are shown in Fig. 1.

NPyr and NPip were frequently found in the samples taken at both locations and NPip was found at concentration levels lower than NPyr. The concentrations for each compound were similar for both city centre and harbour samples. NMor was also found in some samples at both locations but the concentration values in the harbour area were higher than in the city centre.

As mentioned before, there are some studies about the presence of N-nitrosamines in different kind of samples such as house dust, sediments, food, indoor air samples among others, but only few studies about the occurrence of N-nitrosamines in outdoor air samples have been found in the literature. Some of these studies are related with the presence of nicotine and/or their derivatives in cigarette smoke [12,14]. As an example of indoor air samples, De Vocht et al. [33], studied the exposure of NDMA and NMor in a German rubber industry at concentration values of airborne about 0.3 μg m^{-3} for NDMA and 0.23 μg m^{-3} for NMor. Monarca et al. [34] have also monitored indoor air in a rubber industry. In this study, some N-nitrosamines and other semi-volatile compounds

Table 4
Method detection limit (MDL) and method quantification limit (MQL) (expressed in ng m^{-3}), recoveries (%) and repeatability (%RSD, $n=4$) at low and high concentration level of the sample filters for each target compound.

Compound	MDL	MQL	Recovery (%)		Repeatability (%RSD, n=4)	
	(ng m^{-3})	(ng m^{-3})	5 ng m^{-3}	50 ng m^{-3}	5 ng m^{-3}	50 ng m^{-3}
NDMA	0.2	1	49	56	7	3
NMEA	2	5	52	77	18	3
NDEA	0.2	1	76	101	11	8
NDPA	0.15	0.5	83	109	12	6
NMor	0.1	0.2	69	79	4	5
NPyr	0.15	0.5	90	101	6	1
NPip	0.1	0.2	72	85	2	4
NDBA	0.5	1.5	102	107	10	6
Nicotine	0.5	1	93	91	9	1
NDPhA	0.15	1	83	93	7	2

were determined. The results obtained showed that the most frequently compounds determined were NDMA and NMor at concentration values between 0.10 μg m^{-3} and 0.98 μg m^{-3} and between 0.77 μg m^{-3} and 2.40 μg m^{-3}, respectively. Therefore, the results of these studies mentioned before show that one of the most frequent compounds found in air samples is NMor. Moreover, in the present study the presence of NMor in air particulate matter is confirmed but NDMA was not found. This could be explained by the higher volatility of NDMA. Since NMor and nicotine are less volatile, they can be found in both gas phase and air particulate matter.

Up to our knowledge, this is the first time that some of these pollutants with carcinogen effects have been reported in outdoor air particulate matter and this fact makes this study more relevant.

Table 5
Target compounds found at urban and harbour zones, minimum and maximum levels (ng m^{-3}).

Compound	Urban samples			Harbour samples		
	Min (ng m^{-3})	Max. (ng m^{-3})	Freq. (%, $n=6$)	Min (ng m^{-3})	Max. (ng m^{-3})	Freq. (%, $n=12$)
NMor	n.d.	n.q.	83.3	n.d.	0.22	83.3
NPyr	0.3	1.80	100	0.13	1.40	100
NPip	n.d.	0.25	83.3	n.d.	0.22	91.7
Nicotine	4.00	12.5	100	n.d.	3.80	83.3

n.d.: compound not detected (value < MDL); n.q.: compound not quantified (value < MQL)

4. Conclusions

The present study shows the development of a reliable method based on pressurised liquid extraction and gas chromatography/ion trap tandem mass spectrometry for determining the presence of nine N-nitrosamines and nicotine from air particulate matter. This method provides good recovery values for most of

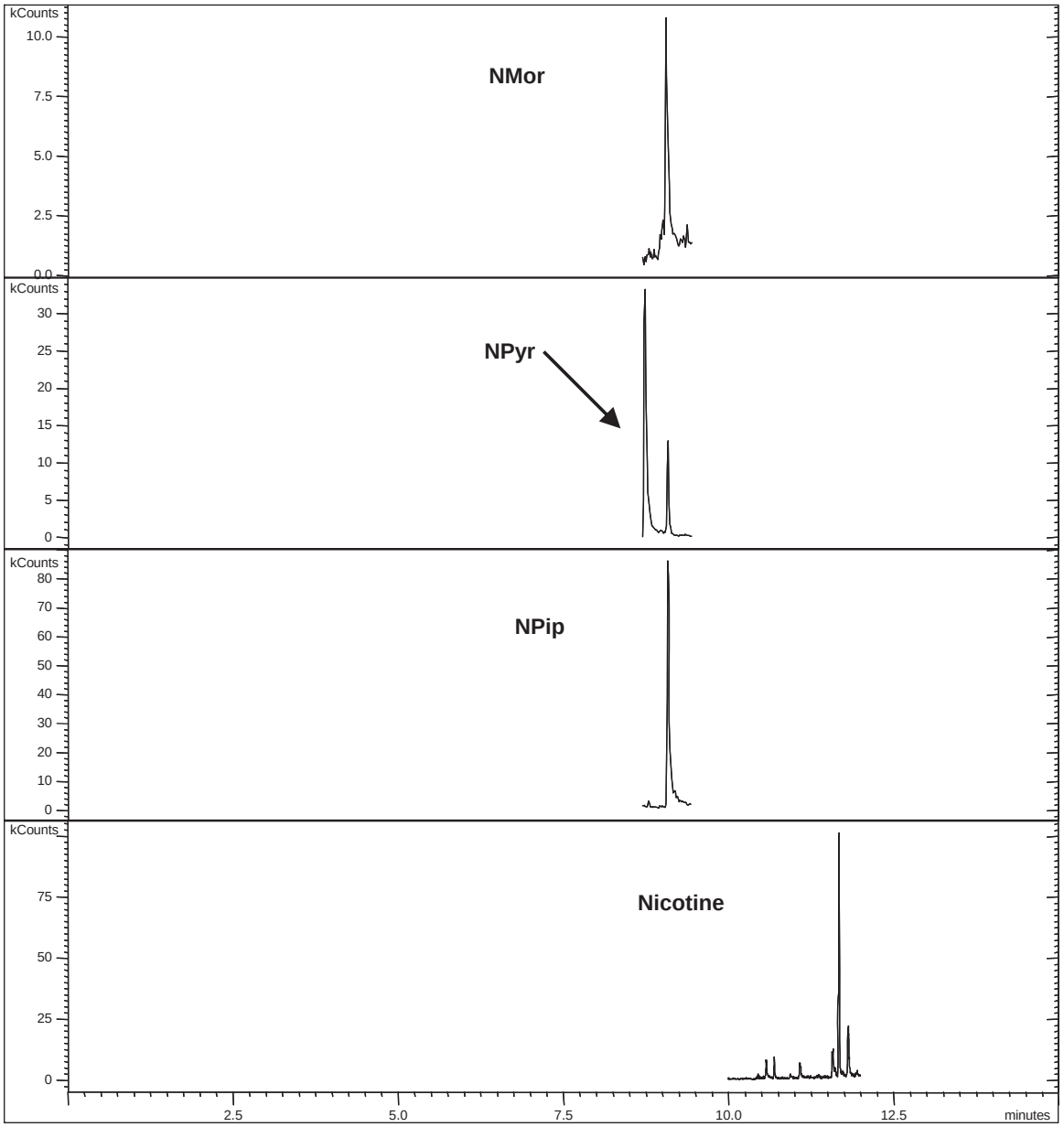


Fig. 1. GC–MS/MS extract ion chromatograms from Tarragona's harbour sample.

these compounds (between 56% and 109%) and a good precision (RSD $<8\%$, $n=4$) with fast extraction and chromatographic analysis (<13 min).

The compounds determined were NMor, NPyr, NPip and nicotine in urban and harbour samples at concentration levels between $<$MQL (NMor) and 12.5 ng m^{-3} (nicotine) and between 0.13 ng m^{-3} (NPyr) and 3.8 ng m^{-3} (nicotine), respectively. This study shows, for the first time, that these N-nitrosamines and nicotine are present in air particulate matter in urban and harbour areas.

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