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Simultaneous determination of alkylphenol ethoxylates and their biotransformation products by liquid chromatography/electrospray ionisation tandem mass spectrometry

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Abstract

Reversed-phase LC–MS/MS is used to determine major estrogenic alkylphenol ethoxylates (APEOs) and their biotransformation products. It allows the simultaneous analysis of eight APEOs, alkylphenoxy carboxylates (APECs) and alkylphenols (APs) in sewage treatment plant (STP) effluents in the same extract after solid-phase enrichment on polymeric Oasis HLB. As precursor ions, $[APEO + NH_4]^+$, $[APEC - H]^-$ and $[AP - H]^-$ were monitored. Instrumental limits of detection (LOD) were 2–600 pg, corresponding to sample concentrations of 0.04–12 ng l^{-1}, without correction for overall method recoveries. Matrix-induced signal suppression during electrospray ionisation (ESI) and extraction as well as overall method recoveries were assessed and the suitability of deuterated surrogates as internal standards was evaluated.
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Keywords: Water analysis; Alkylphenol ethoxylates; Alkylphenoxy carboxylates; Nonylphenol; Octylphenol

1. Introduction

During the last decade, the use of non-ionic surfactants of the alkylphenol ethoxylate (APEO) type has become a focus of interest in public due to the known persistence and estrogenic activity of some biodegradation products generated during wastewater treatment [1,2]. The worldwide production of APEOs has been estimated to be 500,000 t per year [3]. In the last 40 years, APEOs have been used in a variety of applications as detergents or emulsifiers including the production of industrial and household cleaning products. Nowadays, APEOs are increasingly being replaced by alcohol ethoxylates (AEOs) [4,5].

In sewage treatment plants (STPs), biodegradation processes of APEOs are quite complex. Several transformation processes under aerobic and anaerobic conditions have been proposed [6–9] leading to the main biotransformation products depicted in Fig. 1. In addition, alkylphenoxy dicarboxylates (CAPECs) have been reported, proposed to be intermediates from the aerobic biodegradation of alkylphenoxy carboxylates (APECs) [10,11]. Short ethoxy (EO) chain APEOs, APECs and alkylphenols (APs) show estrogenic activity in vitro and cause a number of estrogenic responses in vivo in various aquatic organisms [1,12].

Analytical methods for the determination of APEOs and their biotransformation products have been reviewed with a focus on GC–MS [13,14] and LC–MS [13–15] methodologies. Electrospray ionisation (ESI) is used most often as it offers better sensitivity than atmospheric pressure chemical ionisation (APCI), especially for alkylphenol monoethoxylates (AP1EOs), alkylphenol diethoxylates (AP2EOs) and APs [16].

Most papers published up to now describe for various matrices the LC–MS(/MS) analysis of only part of the analytes determined in this work. Either just APEOs [17–19], APEOs and APs [20,21], or APEOs and APECs [10,22,23] were analyzed, and only few publications report the time-saving enrichment and analysis of APEOs, APECs and APs in the same extract and LC–MS run [11,24]. Some authors report

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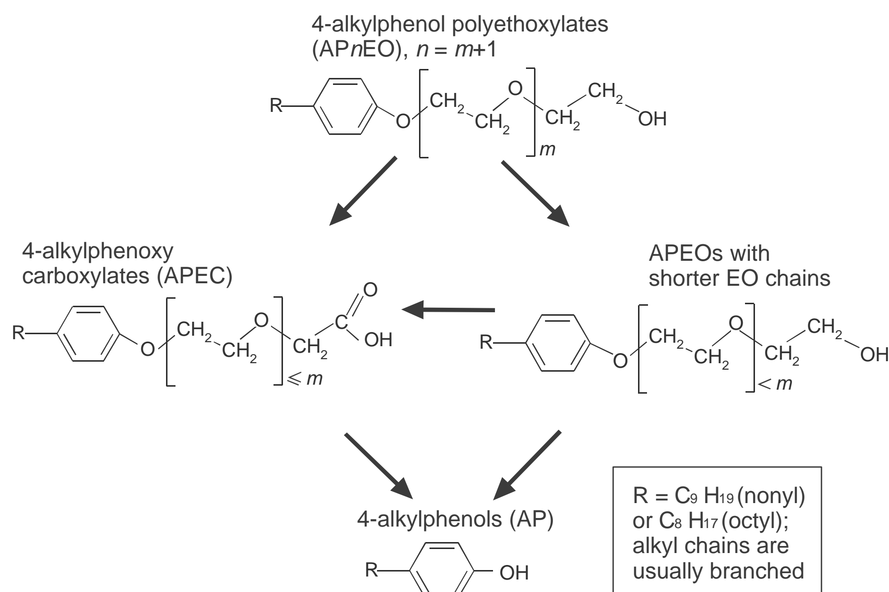

Fig. 1. Biodegradation of alkylphenol polyethoxylates in sewage treatment plants under aerobic/anaerobic conditions.

on the simultaneous enrichment of analytes, but use different LC runs in the positive (PI) and/or negative (NI) ionisation mode [16,25–28]. In those papers reporting on LC–MS/MS determination, substances out of two groups of these compounds are analysed: nonylphenol ethoxylates (NPEOs) and related carboxylic acids (NPECs) [22] or nonylphenol (NP), NPECs as well as related halogenated compounds [23].

This paper presents an LC–ESI–MS/MS method for the simultaneous determination of major NPEOs, octylphenol ethoxylates (OPEOs) and corresponding biotransformation products with estrogenic activity in STP effluents in a single run, after simultaneous solid-phase extraction (SPE). Reversed-phase LC without separation of ethoxymers was used, taking the advantage of higher selectivity of the MS/MS method. For APEOs, $[M + NH_4]^+$ precursor ions were monitored, enhanced by adding ammonium acetate (NH_4Ac) to the LC mobile phases. If no NH_4Ac is added, $[M + Na]^+$ of APEOs give the most intense signals, which are often monitored in single-stage MS applications, but are too stable to allow substantial fragmentation in MS/MS mode [22].

2. Experimental

2.1. Sampling

Three effluent samples were collected in October and November 2002, at the Hamburg STP Koehlbrandhoeft/Dradenau, Germany, having an average population equivalent of 2.1 million. Sewage treatment comprises primary (mechanical) and secondary (biological) treatment, followed by a phosphate elimination step. Sample #1 was a grab sample, while samples #2 and #3 were collected time-proportionally over 24 h. Samples for the analysis of APEOs and biotransformation products were stored in stainless steel barrels previously cleaned with acetone and methanol and filtered with glass fibre filters, GF/C, 1.2 μm, purchased from Whatman International Ltd. (Maidstone, Kent, UK). When sample enrichment was not possible at once, samples were stored at 4 °C overnight, protected from light.

2.2. Chemicals

All standard substances (nonylphenol monoethoxylate (NP1EO), nonylphenol diethoxylate (NP2EO), nonylphenoxy acetic acid (NP1EC), octylphenol monoethoxylate (OP1EO), octylphenol diethoxylate (OP2EO), octylphenoxy acetic acid (OP1EC), 4-*tert*-octylphenol (4-*tert*-OP), D_2-NP1EO, D_2-NP1EC and D_8-4-*n*-NP) were of 96.5% purity or better and were purchased from Dr. Ehrenstorfer GmbH (Augsburg, Germany), except for technical 4-NP, which was of 99.5% purity and was purchased from Riedel-de-Haën (Seelze, Germany). NH_4Ac (Fractopur®), methanol (MeOH, SupraSolv®), acetic acid (p.A., 100%), and ammonium hydroxide solution (p.A., 25%) were obtained from Merck (Darmstadt, Germany). Dichloromethane (DCM) and acetone of Picograde® quality were purchased from Promochem (Wesel, Germany), while de-ionised organic-free water was obtained from a Milli-Q Plus 185™, Elix 5™ system (Millipore, Schwalbach, Germany).

Stock solutions were prepared for all standard substances at 1 mg ml^{-1} in MeOH. Spiking and calibration mixtures at various concentration levels were obtained by combining aliquots of stock solutions and subsequent dilution with MeOH. Calibration solutions were then adjusted to the initial LC eluent composition by adding Milli-Q water and NH_4Ac.

2.3. Solid-phase extraction

Glass columns were packed in-house with the SPE material Oasis HLB® (60 μm bulk material, *N*-vinylpyrrolidone-divinylbenzene copolymer, Waters, Eschborn, Germany) right before enrichment was started. In the optimised method, 400 mg of SPE material was used for 1 l samples, conditioned with 40 ml of MeOH and equilibrated using 40 ml of Milli-Q water. The filtered samples were passed through the pre-conditioned SPE-columns within approx. 1 h, washed successively with 6 ml of Milli-Q water, 6 ml of 2% acetic acid solution with 10% MeOH (v/v) and 6 ml of 2% ammonium hydroxide solution containing 10% MeOH (v/v). The sorbent was then dried for at least 90 min by sucking air through the columns with charcoal filters attached to the inlet of the glass columns to prevent contamination.

The analytes were eluted with 6 ml of MeOH followed by 6 ml of DCM (2–3 ml of MeOH were added at first, drawn into the SPE material and left to infuse for 10 min). Afterwards, the eluate was collected and reduced to less than 1 ml by rotary evaporation and finally reduced to 100 μl under a gentle stream of nitrogen. In order to provide a solvent corresponding to the initial LC conditions, a 100 μl aliquot of 3.0 mM NH_4Ac in Milli-Q water was added.

2.4. LC conditions

Analyses were performed on a HP 1100 Agilent Technologies (Waldbronn, Germany) LC system, consisting of a degasser, binary pump and autosampler. The analytes were separated on a 150 mm × 2.1 mm i.d., 5 μm Zorbax Eclipse XDB-C8 column, preceded by a guard column (12.5 mm × 2.1 mm i.d., 5 μm) of the same packing material, both from Agilent Technologies. The injection volume was 10 μl.

A binary mobile phase gradient with 1.5 mM NH_4Ac in Milli-Q water (A) and MeOH with 1.5 mM NH_4Ac (B) was used at a flow rate of 200 μl min^{-1}: 50% B (3 min)/50% B > 80% B (5 min)/80% B > 100% B (25 min)/100% B (4 min)/100% B > 50% B (3 min), resulting in a run time of 40 min. The system was re-equilibrated for 10 min between runs.

2.5. Mass spectrometry

MS/MS was performed with a triple-stage quadrupole mass spectrometer API 3000 from Applied Biosystems/MDS Sciex (Darmstadt, Germany) equipped with an electrospray probe (Turbo-Ionspray, Applied Biosystems). Nitrogen was used as nebulizer, drying, curtain and collision gas.

Table 1
Tandem mass spectrometric parameters

Analyte	Retention time (min)	Precursor ion (*m/z*)	Declustering potential (V)	Focusing potential (V)	Product ions (*m/z*) (% rel. abundance)	Collision energy (V)
NP	20.9	219.2[a]	−46	−140	133 (100) 147 (12)	−44 −38
D_8-4-*n*-NP	22.3	227.2[a]	−66	−190	112 (100) 126 (2)	−34 −52
NP1EO	21.2	282.2[b]	36	120	127 (100) 71 (26)	13 25
D_2-NP1EO	21.2	284.3[b]	46	130	127 (100) 71 (33)	15 23
NP2EO	21.3	326.3[b]	46	140	183 (100) 121 (12)	17 33
NP1EC	16.4	277.2[a]	−81	−190	219 (100) 133 (26)	−26 −56
D_2-NP1EC	16.4	279.2[a]	−46	−130	219 (100) 133 (19)	−26 −50
4-*tert*-OP	19.1	205.2[a]	−41	−140	133 (100) 117 (9)	−30 −76
OP1EO	19.5	268.2[b]	21	90	113 (100) 139 (12)	13 17
OP2EO	19.5	312.3[b]	51	150	183 (100) 121 (17)	17 31
OP1EC	16.4	263.2[a]	−66	−160	205 (100) 106 (18)	−26 −42

[a] $[M-H]^-$ in NI mode.
[b] $[M+NH_4]^+$ in PI mode.

For each analyte, two parent–product ion transitions were chosen and voltages and gas flows were optimised for maximum intensities. The relevant parameters are given in Table 1. The drying gas temperature in the ESI source was set at 250 °C. Optimised nebulizer, curtain and collision gas flow settings were 9, 10 and 5, respectively; the drying gas flow was 8 l min^{-1}. The ion spray voltage was set at 4800 V in the PI and at −4200 V in the NI mode. Dwell times were adjusted to 100 ms. A typical total ion chromatogram (TIC) and monitored parent–product ion transitions are depicted in Fig. 2.

The 40 min run was divided into three periods. First, the APECs were monitored in the NI mode; the next period comprised 4-*tert*-OP (NI) and OPEOs (PI), while the final period included NPs (NI) and NPEOs (PI).

2.6. Quantification and confirmation

Identification of the compounds was ensured (a) by monitoring two characteristic parent–product ion transitions (quantifier and qualifier, Table 1) for each analyte and (b) by considering a specific time window of elution (mean

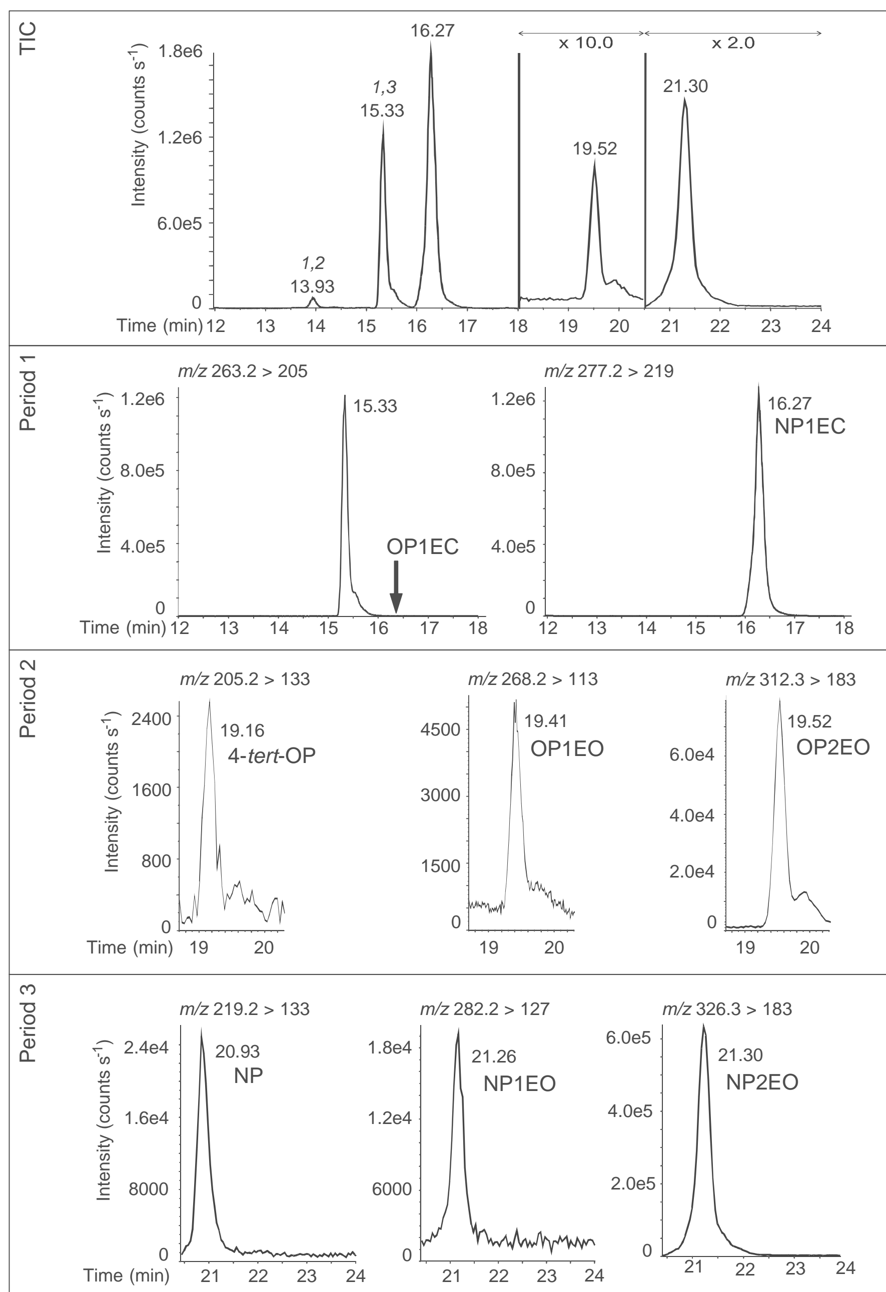

Fig. 2. TIC and parent–product ion transitions (quantifier) of sample #1.

retention time of standards ±30 s). For some analytes in low concentrations, LOQs of qualifier parent–product ion transitions (data not given) were not low enough to allow the confirmation of the concentrations calculated from the corresponding quantifier parent–product ion transitions.

Calibration levels and samples were injected in duplicate. For quantification, a 10-level external calibration, covering three orders of magnitude, was used. Analyte concentrations in STP effluent samples were corrected for the overall method recoveries calculated from spiking experiments (see Section 2.7).

2.7. Recoveries and signal suppression

In order to determine signal suppression, extraction recoveries and overall method recoveries, for each STP effluent sample, six aliquots were processed and analysed: duplicate sets of non-spiked samples (1), samples spiked prior to solid-phase extraction (2) as well as extracts of non-spiked samples spiked prior to LC–MS/MS analysis (3). Spiking levels of samples and extracts were 100–1000 ng l^{-1} (expressed as corresponding sample concentrations) for the individual analytes, adapted roughly to the concentration range of the nonylphenolic analytes in the effluent samples.

Overall method recoveries were calculated from (2) and (1), signal suppression was calculated from (3) and (1). Extraction recoveries were subsequently calculated from overall method recoveries and signal suppression, assuming that additional losses during sample treatment were negligible compared to those during solid-phase extraction.

3. Results and discussion

3.1. Method performance

LC–ESI–MS/MS has a high selectivity as it monitors parent–product ion transitions. This also helps to avoid errors in quantification of APEOs which can occur in reversed-phase LC–MS due to isobaric interferences between singly and doubly charged ammonium or sodium adduct ions of co-eluting ethoxymers [20]. Singly charged APEO adduct ions and doubly charged adduct ions of highly ethoxylated APEOs can have the same nominal *m/z* values, e.g. $[NP1EO + NH_4]^+$ and $[NP7EO + 2NH_4]^{2+}$ with *m/z* 282.2.

3.1.1. Linear range and repeatability

The external 10-level calibration covered three orders of magnitude, with concentrations of the highest calibration level being 1–10 ng μl^{-1}. Calibration curves with weighting $1/x$ were linear in the individual working ranges (limits of detection (LOD)–highest levels) with correlation coefficients between 0.991 and 0.999.

Ten-fold injection of a standard mixture (concentrations: 1.5 ng μl^{-1} for D_8-4-*n*-NP, 1.0 ng μl^{-1} for AP1EOs and 0.5 ng μl^{-1} for other analytes) gave relative standard deviations (RSDs) of peak areas from 1.0% for 4-*tert*-OP to 3.3% for NP1EO. The within-day precision was 2–7% for the individual analytes.

3.1.2. Analytical performance

Four 1 l samples of Milli-Q water were enriched following the procedure described above and analysed with the optimised LC–MS/MS method. For most analytes, blanks were below the limits of detection given in Table 2. Only NP and NP1EC were detectable in some blanks with maximum concentrations of 3 ng l^{-1} (LOD 2 ng l^{-1}) and 0.1 ng l^{-1} (LOD 0.1 ng l^{-1}), respectively.

Instrumental LODs (signal-to-noise-ratio (S/N) = 3) and limits of quantification (LOQs, $S/N = 10$) were estimated from dilution series of standard mixtures, with LOQs being three to four-fold higher than LODs. Typical LODs, which vary slightly with long-term MS performance and matrix-induced signal suppression are listed in Table 2,

Table 2
Instrumental LODs (ng l^{-1}, $S/N = 3$) of the presented method, based on 1 l sample volume and 10 μl injection volume from a final extract volume of 200 μl, without correction for overall method recoveries. Comparison with LODs from other publications

Analyte	LODs (this study)	LODs [26][a]	LODs [24][b]	LODs [16][c]	LODs [29][d]
NP	2.0	11	150	20	8.4
D_8-4-*n*-NP	4				
NP1EO	10	15		100	14.4
D_2-NP1EO	8				
NP2EO	0.2	6		40	13
NP1EC	0.1	13	80	20	86.7
D_2-NP1EC	0.06				
4-*tert*-OP	4			20	6.1
OP1EO	12			100	10
OP2EO	0.1			40	3.3
OP1EC	0.04			20	

[a] $[APEO + Na]^+$-adducts and $[M - H]^-$-ions (APs and APECs) analysed by LC–ESI–MS, two runs.
[b] LC–APCI–MS.
[c] $[APEO + Na]^+$-adducts and $[M - H]^-$-ions (APs and APECs) monitored using LC–ESI–MS, two runs.
[d] GC–MS after derivatization.

Table 3
Analyte concentrations (ng l^{-1}) in effluent samples from the STP Hamburg; samples were processed and analysed in duplicate

Analyte	Sample[a]			Reference[b]			
	1	2	3	[31]	[32]	[33]	[34]
NP	242 ± 1	140 ± 10	141 ± 4	320–1570	250–2300 (561)	25–770 (111)	42–170
NP1EO	175 ± 10	72 ± 6	102 ± 2				
NP2EO	210 ± 10	90 ± 0	166 ± 1		<LOD-5500 (323)		
NP1EC	800 ± 50	1120 ± 15	1010 ± 10		170–5800 (2018)		
4-*tert*-OP	(8 ± 1)	19 ± 1	18 ± 1	281–357		2.2–73 (14)	
OP1EO	17.5 ± 0.2	17 ± 2	15 ± 1				
OP2EO	13 ± 1	13 ± 0	28 ± 1				
OP1EC	<LOD	<LOD	<LOD				

Results for this study are given as arithmetic means ± absolute deviations. Comparison with concentrations in German STP effluents determined in other studies.

[a] This study ($n = 2$), value with $S/N < 10$ given in brackets.

[b] Concentration ranges from other studies, medians given in brackets.

being comparatively high in case of AP1EOs, which is in line with findings of other studies [11,25]. Method detection limits (MDLs) were not determined, but are expected to be in the same range as instrumental LODs due to the high selectivity of MS/MS analysis, which is supported by the results for STP effluent samples (Table 3) where OP1EO could be quantified in all samples at concentrations below the instrumental LOQ.

The comparison of our instrumental LODs with those reported in other studies is restricted because of different sample matrices, the spectrum of analytes and the reported information on LODs and how they were derived. Concerning methods which allow the determination of selected APEOs, APECs and APs in aqueous samples, LODs of the presented LC–ESI–MS/MS method for individual analytes are mostly lower and in some cases in the same range as in other studies (Table 2).

3.1.3. Recoveries and signal suppression

Overall method recoveries, signal suppression and extraction recoveries for STP effluent samples are depicted in Fig. 3. They were calculated as described in Section 2.7 from the results of duplicate sets of samples and are presented as arithmetic means and RSDs ($n = 6$). Overall method recoveries ranged from 25 (NP) to 47% (OP1EO), with the exception of one deuterated standard (15%, D_8-4-*n*-NP). Signal suppression was found to be high for all analytes due to the complex matrix: 39% (NP1EO) up to 72% (OP1EC). Extraction recoveries were between 65 (NP2EO) and 110% (NP1EC), except for D_8-4-*n*-NP (43%).

In addition, one set of extracts of sample #2 and two sets of extracts of sample #3 were analysed after four-fold dilution, data included in Fig. 3 ($n = 3$). The overall method recoveries increased up to two-fold compared to the results of undiluted extracts, and ranged from 50 (NP2EO, OP1EC) to 75% (4-*tert*-OP) with the exception of D_8-4-*n*-NP (29%). This is caused by clearly decreased signal suppression of 16 (4-*tert*-OP) up to 39% (D_2-NP1EC), with the exception of D_8-4-*n*-NP (43%) and OP1EC (50%). Although improving overall method recoveries, the lower enrichment factor causes two to four-fold increased LODs.

Three commercially available deuterated compounds, D_2-NP1EO, D_2-NP1EC and D_8-4-*n*-NP were also studied, with results included in Fig. 3. As expected, D_2-NP1EO and D_2-NP1EC showed recoveries and signal suppression comparable with their non-deuterated analogues NP1EO and NP1EC, respectively. However, there are noticeable differences compared with the other APEOs and OP1EC in their performance during SPE and LC–MS/MS detection. For D_8-4-*n*-NP, extraction recoveries are significantly lower than for branched NP and 4-*tert*-OP. From these preliminary results it can be concluded, that thorough testing of these deuterated substances is needed before using them as internal standards for quantification. At least in our method, D_8-4-*n*-NP is not applicable to correct for overall method recoveries of branched NP and 4-*tert*-OP.

3.2. Application to STP effluents

Concentrations of APEOs, APECs and APs in STP effluent samples were corrected for overall method recoveries and are listed in Table 3. The results for analyses of diluted extracts (data not shown) were in good agreement with results for non-diluted extracts. With the exception of OP1EC, the analytes were found in all STP effluent samples, NP-derivatives having about one order of magnitude higher concentrations than the octylphenolic analogues. This is likely due to the fact that 80–90% of APEOs produced worldwide are NPEOs, while the remaining part mainly consists of OPEOs [3,30]. Highest concentrations were determined for NP1EC (800–1120 ng l^{-1}), which is a major biotransformation product of NPEOs, formed during aerobic wastewater treatment. These relatively high concentrations in the STP effluents can partly be explained by the higher solubility in water of APECs compared to APs and APEOs, which tend to adsorb to sewage sludge and are more efficiently removed during wastewater treatment.

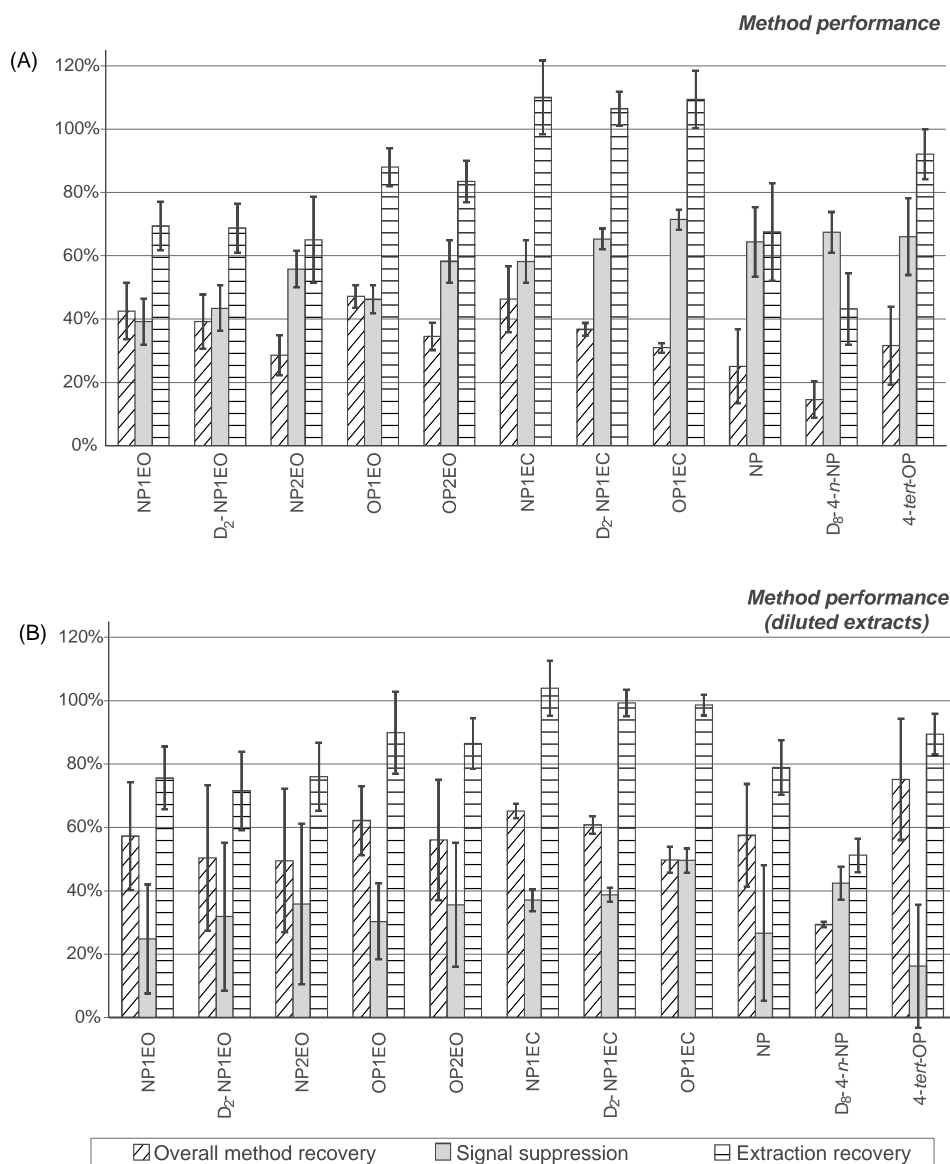

Fig. 3. Method performance (overall method recovery, signal suppression and extraction recovery) calculated from spiking experiments of duplicate sets of STP effluent samples. Results are shown as arithmetic means and RSDs, details see text. (A) Undiluted extracts ($n = 6$); (B) four-fold diluted extracts ($n = 3$).

Concentrations of APEOs and their degradation products in STP effluents vary widely in different countries as has been reviewed recently by Ying et al. [8], probably for several reasons as due to different application volumes and differing sewage treatment processes. Our results are within the concentration ranges reported for some analytes in German STP effluents (Table 3).

4. Conclusions

SPE and LC–ESI–MS/MS as described in this work allow the simultaneous enrichment and determination of eight major estrogenic APEOs and biotransformation products. With the sensitivity and selectivity provided, it is most useful for the analysis of STP effluents. The method can be extended to cover additional analytes; however this would reduce sensitivity, as more parent–product ion transitions would have to be monitored in each period.

For high enrichment factors, matrix interferences are distinct and have to be controlled by standard addition to sample aliquots or by using internal standards. As could be shown by means of diluted sample extracts, a lower enrichment factor leads to significantly reduced signal suppression due to lower matrix effects. Nevertheless, without the high enrichment factor of 5000, LOQs would not be sufficient for the determination of typical concentrations especially of NP1EO and 4-*tert*-OP in effluent samples. Concentrations

of APEOs and biotransformation products in effluents of the STP Hamburg were in the same range as reported for other STPs in Germany. However, the comparison was limited to only few data published for branched 4-NP, 4-*tert*-OP, NP2EO and NP1EC.

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