

Bisphenol A and other alkylphenols in the environment - occurrence, fate, health effects and analytical techniques

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Abstract. Bisphenol A and other alkylphenols are widely used in plastic and other industrial consumer products. Release of these compounds into the aquatic environment during their manufacture, use and disposal has been a great scientific and public concern due to their toxicity at high concentrations and endocrine disrupting effects at low concentration on aquatic wildlife and human beings. This paper reviews the published data and researches on the environmental occurrence, distribution, health effects and analytical techniques of bisphenol A and alkylphenols. The aim is to provide an overview of the current understanding about bisphenol A and alkylphenols in the environment and the difficulties faced today in order to establish standard and systematic environmental analysis and assessment process for these endocrine disruptor compounds.

Keywords: bisphenol A; alkylphenols; environmental fates; environmental endocrine disruptors; gas chromatography-mass spectrometry; high-performance liquid chromatography; liquid-liquid extraction

1. Introduction

During the past few decades, concerns have been raised on the changes in the health and fecundity of human and wildlife associated with the disruption of endocrine systems by environmental chemicals (Bergman *et al.* 2012, Chen *et al.* 2013, Zuo *et al.* 2006, 2013). It has been proposed (Pedersen and Lindholm 1999) that many high volume industrial chemicals, already found in high concentration both on land and in the aquatic environment, may have adverse effects on the endocrine systems in humans and animals. Among these high-volume chemicals are alkylphenols (APs) and in particular bisphenol A. The chemical structures of the alkylphenols interested in this study are presented in Fig. 1.

Alkylphenols were first found to be oestrogenic (oestrogen-mimicking) in the 1930s (Dodds *et al.* 1938), and further evidence to support this finding was published in 1978 (Mueller and Kim 1978). The concentration levels of APs now present in the environment may be well above the threshold necessary to induce endocrine disruption in wildlife. Alkylphenolic compounds have been detected in air, water, sediment, soil and biota at various levels in many parts of the world. Therefore, in order to assess the environmental effects of these substances, it is necessary to

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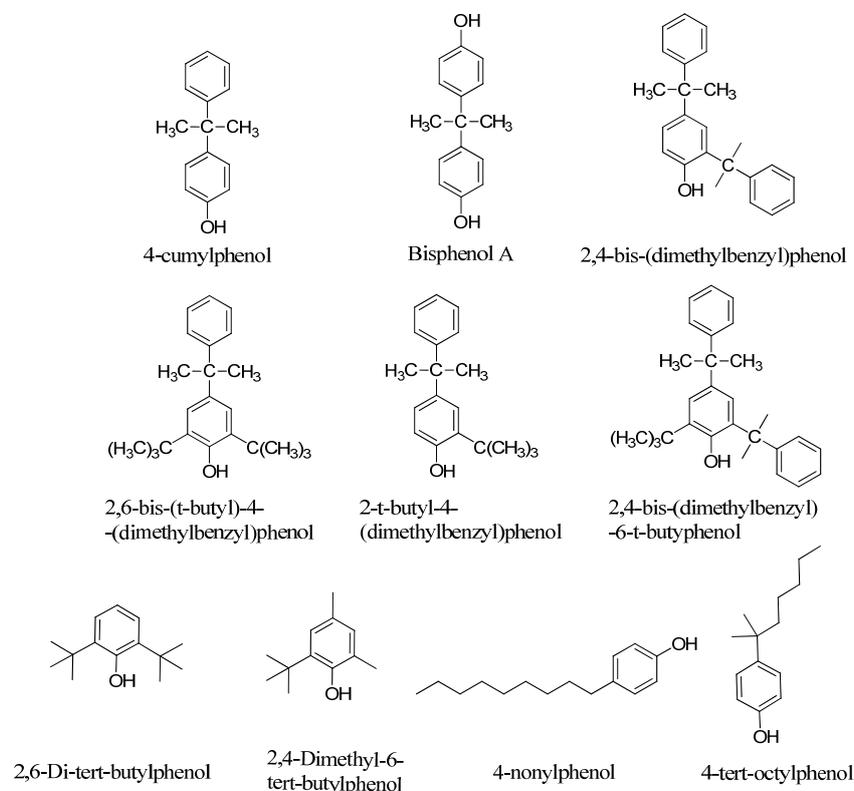


Fig. 1 Chemical structures of bisphenol A and other alkylphenols

understand the distribution, environmental fate, health effects on human and wildlife of APs and their metabolites in the environment.

2. Uses and exposure of alkylphenols

Alkylphenols (APs) are a family of organic compounds synthesized through the alkylation of phenols. Alkylphenols are used extensively in the detergent, fuel and lube additive, polymer additive, polymer manufacture, and phenolic resin industries. These compounds are also used as building block precursors in making fragrances, thermoplastic elastomers, antioxidants, oil field chemicals and fire retardant materials. Through the downstream use in manufacture as alkylphenolic resins, alkylphenols are found in tires, adhesives, coatings, carbonless copypaper and high performance rubber products. APs have been in industrial use for more than 60 years.

2.1 Bisphenol A

In the 1950s, BPA was discovered as a chemical to make polycarbonate plastics, which commonly used in food industries (Talsnessl *et al.* 2009). The BPA contamination in food, particularly canned food and beverage, has been a great concern because of its endocrine

disrupting property. Although Japanese cans industries introduced the BPA free plastic formulation to manufacturing line in the late 1990s (Ballesteros-Gómez *et al.* 2009), BPA is still widely used as a base compound in the resin lining of food and beverage cans in the USA and many other countries. Another common use of BPA is as monomer of dental sealants and filling composites. BPA is also used in printer ink, to coat paper for receipts and as plasticizer in Polyvinyl Chloride (PVC) plastic products.

2.2 4-cumylphenol

4-cumylphenol (4-CP) is used as raw materials in manufacture resins. The growth in 4-CP production is expected to parallel the growth rate of polycarbonates, particularly the grades used to produce compact discs (Lorenz *et al.* 1992). Since the chemical can react with ethylene oxide to form a non-ionic surfactant, 4-cumylphenol is also used as surfactant raw materials (Rudel *et al.* 2003). Another application of 4-cumylphenol is for fungicide, because of the strong anti-mildew characteristic for the compound (Mark 1981). Besides that, this compound is also used as a molecular regulator of epoxy resin, reactive diluents, incremental agent, plasticizer and stabilizer for industries (Messina *et al.* 1984), and also serves as the polycarbonate for molecular weight regulator agent (Mark 1979).

2.3 2,6-Di-tert-butylphenol & 2,4-Dimethyl-6-tert-butylphenol

These two organic compounds and their derivatives are used industrially as UV stabilizer. They are also used in hydrocarbon-based products, like fuels, gasolines, avgas and plastics, as antioxidants. 2,4-Dimethyl-6-tert-butylphenol is suspected to be respiratory toxic and neurotoxic (Fiege *et al.* 2002).

2.4 nonylphenol and octylphenol

Nonylphenol and octylphenol were both used in industries as a precursor of commercially important detergents. After ethoxylation, these compounds are widely used as industrial surfactants, as emulsifiers for emulsion polymerization, as laboratory detergents and as pesticides. It's reported that millions of kilograms of nonylphenols were produced annually (Fiege *et al.* 2002).

2.5 2,4-bis-(dimethylbenzyl)phenol

2,4-bis-(dimethylbenzyl)phenol (2,4-DCP) is used in antioxidant mixtures and in surfactant formulations (Russell *et al.* 2002). This chemical may also be released into environment upon hydrolysis of the antioxidant plasticizer bis-(2,4-Dicumylphenyl)pentaerythritol diphosphite (tradename: Doverphos) (Bobsein *et al.* 2007).

2.6 2,6-bis-(t-butyl)-4-(dimethylbenzyl)phenol

This compound was firstly developed by Monsanto as a juvenile hormone mimics, named MON-0585 and later applied as a mosquito insecticide (Jakob and Schoof 1972). Like BPA and other alkylphenolic compounds, 2,6-bis-(t-butyl)-4-(dimethylbenzyl)phenol is also used in industry as antioxidant in polymer manufacture (Russell *et al.* 2002).

2.7 2-t-butyl-4-(dimethylbenzyl)phenol and 2,4-bis-(dimethylbenzyl)-6-t-butylphenol

These two chemicals are used in industries as antioxidant blends for rubber and other polymer manufacture. 2,4-bis-(dimethylbenzyl)-6-t-butylphenol, under the tradename of isobutyleneated methylstyrenated phenol, is reported as a high volume production chemical (more than 1 million pounds/year) from the EPA as other alkylphenols discussed above.

The investigation on the toxicity of these alkylphenolic compounds has been encouraged by many research program and governmental organizations (U.S. EPA 2002).

3. Relevant physicochemical properties

The physicochemical properties determine the behaviour of APs in the environment. From the physicochemical data, such as solubility and partition coefficient, we can predict the partitioning behaviour of these chemicals among different phases (air, water and sediment/soil) in the environment. Table 1 presents the relevant physicochemical properties of APs. From the data in Table 1, APs and BPA are considered to be hydrophobic due to their high Log K_{ow} value (octanol-water partition coefficient greater than 4, except BPA is 3.45), which represents the high tendency for these chemicals to partition into an organic phase (e.g., fish, soil) rather than an aqueous phase. In other words, APs and BPA tend to have low water solubilities, large soil/sediment adsorption coefficients, and large bioaccumulation factors for aquatic life.

According to the data, alkylphenolic compounds could easily distribute into soil or sediment in an aquatic environment. Because of the persistence, toxicity and bioaccumulation of the APs and BPA, there are more and more concerns about their presence in the environment. Table 2 shows the assessment of environmental fate of BPA and other APs by Fugacity Modeling (Cash 1995).

4. Distribution in the environment

Since APs are not produced naturally, the presence of APs in the environment is solely a consequence of anthropogenic activities. Industrial and municipal wastewater treatment plant effluents are the primarily pollution source of APs in aquatic environment (Ying *et al.* 2002). APs can also enter the environment through direct discharge such as pesticide application. Table 3 collected information on the occurrence and distribution of BPA and other APs in various environments, including ambient air, water, soil, sediments and biota together with the analytical methods used for the determination.

4.1 Air

The vapor pressure and Log K_{OA} values (octanol-air partition coefficient) are relatively low for APs and BPA, which lead to just fairly small fraction of these chemicals entering the atmosphere from the aqueous phase or surface soil. However, some alkylphenols were still being detected in atmospheric samples. Dachs *et al.* (1999) first reported the occurrence of nonylphenol in the atmosphere, and found the concentrations ranging from 2.2 to 70 ng/m³ in samples that taken near the Hudson River. Van Ry *et al.* (2000) studied the seasonal trends of alkylphenols in the atmosphere of the Hudson River, and indicated the concentrations of nonylphenol (NP) and

Table 1 Physicochemical properties of alkylphenols in environmental samples

Parameter	Molar mass (g/mol)	Boiling point (°C)	Water solubility (mg/L)	Log K_{OW}^a	Henry's law constant ^a (atm m ³ /mol)	Vapor pressure ^a (mmHg)	Log $K_{OA}^{a,b}$	Log K_{OC}^c	Log BCF ^d	Acute Toxicity to Fish 96 h-LC ₅₀ ⁿ (mg/L)
BPA ^{e,f,g}	228.29	220	120	3.32	3.95e-10	4.60e-05	12.8	4.88	1.86	4.6
4-cumylphenol ^h	212.29	335	23.52	4.12	1.89e-07	1.81e-04	9.56	4.67	2.48	0.25
2,6-Di-tert-butylphenol ^{i,j}	206.32	253	2.5	4.92	1.97e-04	9.42e-03	8.74	4.15	2.64	0.74-10
2,4-Dimethyl-6-tert-butylphenol ^k	178.27	249	29.64	4.52	9.57e-05	4.48e-02	8.66	3.72	2.33	
4-Octylphenol ^k	206.32	310	3.11	5.50	8.51e-06	9.76e-05	9.24	4.52	2.53	0.25
4-Nonylphenol ^{l,m}	220.35	293	6.35	5.76	1.27e-04	2.36e-05	8.62	4.78	2.74	0.13-0.31
2-t-butyl-4-dimethylbenzylphenol ^k	268.39	363	0.500	6.03	1.07e-06	1.58e-05	11.1	5.53	3.50	
2,6-bis-(t-butyl)-4-(dimethylbenzyl)phenol ^k	324.50	398	0.029	7.09	1.53e-06	1.94e-06	11.7	9.39	4.23	
2,4-bis-(dimethylbenzyl)phenol ^k	330.46	436	0.055	6.73	4.63e-08	1.93e-07	13.0	6.91	4.04	0.02
2,4-bis-(dimethylbenzyl)-6-t-butylphenol ^k	386.57	471	0.003	7.79	5.30e-08	2.22e-08	13.6	7.78	3.27	

^a Water solubility, log K_{OW} , Henry's law constant, vapor pressure,

Log K_{OA} , are all obtained in 25°C.

^b Log octanol-air partition coefficient

^c soil adsorption coefficient

^d Log BCF, bioaccumulation estimate

^e Dorn *et al.* 1987

^f Hansch and Leo 1995

^g Cousins *et al.* 2002

^h Chiha *et al.* 2011

ⁱ Geyer *et al.* 1981

^j Hansch and Leo 1995

^k Predicted data, generated by EPISuite™

^l Shiu *et al.* 1994

^m Itokawa *et al.* 1989;

ⁿ 96-hour LC₅₀ for fish, Staples *et al.* 1998, U.S. EPA 2009

Table 2 Model Assessment Results of the Environment Fate of APs and BPA

Mass amount (%)	BPA	4-Cumylphenol	2,6-Di-tert-butylphenol	2,4-dimethyl-6-tert-butylphenol	4-Octylphenol	4-Nonylphenol	2-t-butyl-4-(dimethylbenzyl)phenol	2,6-bis-(t-butyl)-4-(dimethylbenzyl)phenol	2,4-bis-(dimethylbenzyl)phenol	2,4-bis-(dimethylbenzyl)-6-t-butylphenol
Air	9.24e-5	0.166	0.173	0.403	0.321	0.403	0.0785	0.0885	0.0316	0.0614
Water	11.9	15.1	12.3	14.9	12.4	14.9	3.9	1.49	1.64	1.33
Soil	87.5	80.0	63.9	73	48	73	36.3	32.9	35.0	34.1
Sediment	0.566	4.72	23.6	11.7	39.3	11.7	59.7	65.6	63.3	64.5

tert-octylphenol (t-OP) are higher in summer than fall and early winter. The authors also stated that the occurrence of the APs in the atmosphere is an important environmental issue in urban, industrial coastal-impacted area.

4.2 Wastewater and surface water

4.2.1 Wastewater

Although APs are highly treatable and can be mostly eliminated in well-functioning waste water treatment plants, they still have been detected in effluents of many municipal sewage treatment plants (STPs). Alkylphenols and BPA have been detected, typically in the range of micro gram per liter, in the influent and effluent of many wastewater treatment plants in numerous locations worldwide (Barber *et al.* 2007, Espejo *et al.* 2002, Céspedes *et al.* 2008, Cantero *et al.* 2006, Isobe *et al.* 2001, Sánchez-Avila *et al.* 2009). According to the authors, the effluents of wastewater treatment plants are considered to be the most common route for APs entry into the environment. Bennie *et al.* (1997) observed that the concentrations of an alkylphenolic compounds in natural waters and sediments are higher near the outfalls from wastewater treatment plants. Bennett and Metcalfe (1998) also determined that APs concentrations in sediment were high near urban and industrialized areas.

4.2.2 Surface water

Due mainly to the discharge of effluents from wastewater treatment plants (both industrial and municipal STPs), the occurrence of APs have been widely reported in surface waters (rivers, lakes and coastal waters as well as aquatic biota) around the world (Ahel *et al.* 1996, 2000, Bennie *et al.*

Table 3 Distribution, analytical techniques of alkylphenols in environmental samples

Source	Location	Pretreatment	Method	Concentration	Reference
Air	Hudson River Valley	Adsorbing by PUF foam/quartz fiber filter/XAD-2 resin; followed Soxhlet extraction	GC-MS	2.2 to 70 ng/m ³ (NPs)	Dachs <i>et al.</i> 1999
Air	Hudson River Valley	Adsorbing by PUF foam/quartz fiber filter/XAD-2 resin; followed Soxhlet extraction	GC-MS	LOD to 81 ng/m ³ (NPs) <LOD to 2.5 ng/m ³ (OPs)	Van Ry <i>et al.</i> 2000
Air	North Sea	Adsorbing by PUF/XAD-2 column, quartz fiber filter; followed Soxhlet extraction, silica gel clean-up & derivatization	GC-MS	0.002 to 0.42 ng/m ³ (NPs)	Xie <i>et al.</i> 2006
Wastewater (effluent)	Metropolitan	Acidification; followed liquid-liquid extraction	GC-MS	0.34 to 1.7 µg/L (NP) 0.17 to 57 µg/L (OP)	Barber <i>et al.</i> 2007
Wastewater	Aire Geneva (Switzerland)	Liquid-liquid extraction	GC-MS/ LC-MS	1.0-6.8 µg/L (NP)	Espejo <i>et al.</i> 2002
Wastewater (effluent)	Spain	SPE(RP-18 cartridge)	LC-MS	<LOD to 5.67 µg/L (NP) <LOD to 0.29 µg/L (OP)	Céspedes <i>et al.</i> 2008
Wastewater (effluent)	Canada City (Spain)	SPE (SDS hemimicelle-based cartridge)	LC-MS	20 to 54 µg/L (NP) 4.1 to 16 µg/L (OP)	Cantero <i>et al.</i> 2006
Wastewater (effluent)	Metropolitan (Tokyo)	SPE (C ₁₈ cartridge); followed silica gel clean-up	GC-MS	0.08 to 1.24 µg/L (NP)	Isobe <i>et al.</i> 2001
Wastewater (influent & effluent)	Maresme (Catalonia, Spain)	SPE (Oasis HLB cartridge)	GC-MS	102 ± 50 µg/L (NP, influent) 21.9 ± 32 µg/L (NP, effluent)	Sánchez-Avila <i>et al.</i> 2009
Natural mineral waters	French	SPE (C ₁₈ cartridge) & SPE (HF-PSA cartridge)	LC-MS-MS	<LOQ	Dévier <i>et al.</i> 2013

River	Great Lakes basin & St. Lawrence River	Acetylation (acetic anhydride); followed liquid-liquid extraction	GC-MS	<0.01 to 0.92 $\mu\text{g/L}$ (NP) <0.005 to 0.084 $\mu\text{g/L}$ (OP)	Bennie <i>et al.</i> 1997
River & Lake	Lake Biwa (Japan)	Liquid-liquid extraction	GC-MS	LOD to 0.09 $\mu\text{g/L}$ (OP)	Tsuda <i>et al.</i> 2000
River	Edogawa River & Sakagawa River (Tokyo)	Liquid-liquid extraction	GC-MS	0.12 to 9.5 $\mu\text{g/L}$ (NP) <LOD to 1.7 $\mu\text{g/L}$ (OP)	Watanabe <i>et al.</i> 2007
River	Tama River (Japan)	Stir Bar Sorptive extraction (SBSE; polydimethylsiloxane stir bar); subjected to thermal desorption with <i>in tube</i> silylation	GC-MS	55.1 to 59.7 $\mu\text{g/L}$ (NP) 12.6 to 18.2 $\mu\text{g/L}$ (OP)	Kawaguchi <i>et al.</i> 2005
River	Anoia Rivers & Cardener Rivers (Spain)	SPE (RP-18 cartridge)	LC-MS	LOD to 644 $\mu\text{g/L}$ (NP)	Sole <i>et al.</i> 2000
River	Ebro River Basin (Spain)	SPE (Oasis HLB cartridge)	GC-MS	<LOD to 2.575 $\mu\text{g/L}$ (BPA) <LOD to 24.288 $\mu\text{g/L}$ (NP) <LOD to 1.542 $\mu\text{g/L}$ (OP)	Navarro <i>et al.</i> 2010
River	Glatt River, Thur River & Rhine River	steam distillation/solvent extraction	HPLC (normal phase)	0.025 to 0.3 $\mu\text{g/L}$ (NP)	Ahel <i>et al.</i> 1993
River	Glatt River	steam distillation/solvent extraction	HPLC (normal phase)	0.7 to 26 $\mu\text{g/L}$ (NP)	Ahel <i>et al.</i> 1996
River and estuary	Aire River	SPE (C ₁₈ cartridge)	GC-MS	0.2 to 180 $\mu\text{g/L}$ (NP)	Blackburn and Waldock 1995
River	Taiwan	Graphitized carbon black (GCB) cartridge extraction	GC-MS	1.8 to 10.0 $\mu\text{g/L}$ (NP)	Ding <i>et al.</i> 1999

River	Pearl River Delta (China)	SPE(C ₁₈ cartridge)	GC-MS	<LOD to 0.628 µg/L (NP) <LOD to 0.068 µg/L (OP)	Chen <i>et al.</i> 2006
River	Poland	Dispersive liquid-liquid microextraction (DLLME, dispersing solvent-acetone, extracting solvent- trichloroethylene)	HPLC-fluorescence	<LOQ (NP) 0.1 ± 0.01 (OP)	Zgola-Grzeszkowiak 2010
Sea water/surface water/drinking water	Galicial, NW Spain	Membrane assisted solvent extraction (membrane: polypropylene, extraction solvent: hexane)	LC-MS-MS	<LOD to 0.019 µg/L <LOQ to 0.19 µg/L	Salgueiro-González <i>et al.</i> 2013
Surface water	San Francisco Bay	Digested in methanolic KOH; LLE (hexane); after derivatisation clean up by silica column chromatography	GC-MS	<LOQ to 72.9 (4-NP)	Klosterhaus <i>et al.</i> 2013
Water from oil platforms	North and Norwegian Seas	SPE (anion-exchange sorbent)	GC-MS	2450 to 349997 µg/L (total alkylphenol)	Boitsov <i>et al.</i> 2007
Sewage sludge	Netherlands	Soxhelt extraction; followed SPE (C ₁₈ cartridge) and adsorption chromatographic column (clean up)	HPLC/GC-MS	<LOD to 682.2 mg/kg (NP)	de Voogt <i>et al.</i> 1997
STP sludge	Canada	Supercritical Fluid Extraction (SFE)	HPLC	28 to 304 µg/g (NP)	Lee <i>et al.</i> 1997
STP sludge	Spain	Accelerated solvent extraction (ASE, 1:1 acetone/hexane); followed SPE (C ₁₈ cartridge) for purification	LC-MS (CI-MS)	105 to 238 µg/kg (OP) 142 to 500 µg/kg (NP)	Andreu <i>et al.</i> 2007
STP sludge	Spain	ASE (1:1 acetone/methanol); followed SPE (C ₁₈ cartridge) for purification	HPLC-MS	66.5 to 194 µg/g (NP) 1.91 to 9.04 µg/g (OP)	Céspedes <i>et al.</i> 2008

Farms' fields sludge	Hangzhou, China	ASE (acetone); followed SPE (C ₁₈ cartridge) for clean-up	UPLC-MS	0.31 to 6.50 mg/kg (4-NP) 0.19 mg/kg (4-OP) 0.088 mg/kg (4-tert-OP)	Wang <i>et al.</i> 2009
Sediment	Boston Harbor	Microwave extraction; followed SP (polystyrene-divinylbenzene resin) for purification	GC-MS/LC-UV/LC-MS	11.4 to 12.5 ng/g (OP) <LOD to 22.9 ng/g (NP) 1.5 to 28.3 ng/g (BPA)	Stuart <i>et al.</i> 2005
Sediment	Bingley, River Aire and Tees & Mersey Estuaries	Ultrasonic extraction; followed SPE(C ₁₈ cartridge) for purification	GC-MS	1 µg/g to 15 µg/g (NP)	Blackburn <i>et al.</i> 1999
Sediment	Ebro River Basin	ASE (hexane:dichloromethane)	GC-MS	69.00-5998.92 µg/kg (NP) 1.22-143.13 µg/kg (OP) 57.95 µg/kg (BPA)	Navarro-Ortega <i>et al.</i> 2010
Sediment	San Francisco Bay	Digested in methanolic KOH; LLE (hexane); after derivatisation clean up by silica column chromatography	GC-MS	21.5 to 86.3 (4-NP)	Klosterhaus <i>et al.</i> 2013
Fish and shellfish	Lake Biwa (Japan)	Liquid-liquid extraction; followed by adsorption chromatographic purification	HPLC	<LOD to 19 ng/g (NP) <LOD to 5 ng/g (OP)	Tsuda <i>et al.</i> 2000
Ayu Sweetfish	Tama River (Japan)	Liquid-liquid extraction; followed by adsorption chromatographic purification	GC-MS	<LOD to 110 ng/g (NP) <LOD to 6 ng/g (OP)	Tsuda <i>et al.</i> 1999
fish	River Aire (UK)	Soxhlet extraction; followed SPE for clean up	GC-MS	<LOD to 0.8 µg/g (NP)	Blackburn <i>et al.</i> 1999
Crustacean and fish	Adriatic Sea (Italy)	Liquid-liquid Extraction; followed derivatisation	GC-MS	9.5 to 1431 ng/g (NP) 0.3 to 4.7 ng/g (OP)	Ferrara <i>et al.</i> 2005
Prawn	MA, USA	Liquid-liquid Extraction	GC-MS	0.67-5.51 ng/g (BPA) 0.36-1.61 ng/g (2,4-DCP) <LOD to 1.96 ng/g (4-CP)	Zhu and Zuo 2013

Mulletts, seabreams, shrimp, hakes, anchovies and tuna	Tyrrhenian Sea	Liquid-liquid Extraction; followed derivatisation	GC-MS	34 to 55 ng/g (total APs)	Ferrara <i>et al.</i> 2008
Mussels	San Francisco Bay	Steam extraction (isooctane) followed SPE (aminopropyl cartridge)	LC-MS-MS	<LOQ to 94.5 (4-NP)	Klosterhaus <i>et al.</i> 2013
Sea food	Yanji, Jilin province, China	Liquid phase microextraction (acceptor phase: 0.1 M potassium hydroxide solution)	HPLC-UV	<LOQ to 14.0 ng/g (4-n-BP) 26.0-86.1 ng/g (t-op) 45.0-180.4 ng/g (NP)	Yang <i>et al.</i> 2013
Commercial meat	Beijing, China	ASE(acetone); followed SPE (amino-propyl cartridge) for clean up	LC-MS-MS	0.49 to 55.98 µg/kg (NP)	Shao <i>et al.</i> 2007
Milk	UK	Liquid extraction (CH ₂ Cl ₂); followed gel-permeation chromatography for purification	GC-MS	30 to 1000 µg/kg (NP)	Rhind <i>et al.</i> 2007
Beverage	Beijing, China	SPE (Oasis HLB cartridge)	LC-MS-MS	36.4 to 464.6 ng/L (NP) 25.3 ng/L (OP)	Shao <i>et al.</i> 2005
Breast milk and commercial milk	Taiwan	Liquid-liquid extraction (hexane); followed SPE (HLB cartridge) for clean up	GC-MS	1.7 to 11.6 ng/g (4-NP) 0.4 to 1.1 ng/g (4-OP)	Lin <i>et al.</i> 2009
Baby food	Taiwan	Steam distillation extraction	GC-MS	1.9 to 21 ng/g (4-NP) 0.6 to 19 ng/g (4-t-OP)	Li <i>et al.</i> 2008
Bottle water	Greece	Liquid-Liquid extraction (dichloromethane)	GC-MS	4.6 to 112 ng/L (BPA) 7.9 ng/L (NP) <2.0 ng/L (t-OP)	Diana and Dimitra 2011
Human Cord blood	Malaysia	SPE (C ₁₈ cartridge)	GC-MS	<LOD to 15.17 ng/mL (NP) <LOD to 4.05 ng/mL (BPA) <LOD to 4.17 ng/mL (4-n-OP) <LOD to 1.15 ng/mL (4-t-OP) <LOD to 0.80 ng/MI (4-n-butylphenol) <LOD to 0.54 ng/mL (4-n-hexylphenol)	Tan and Mohd 2002

1997, Blackburn and Waldock 1995, Boitsov *et al.* 2007, Chen *et al.* 2006, Ding *et al.* 1999, Kawaguchi *et al.* 2005, Klosterhaus *et al.* 2013, Navarro *et al.* 2010, Salgueiro-González *et al.* 2013, Sole *et al.* 2000, Tsuda *et al.* 2000, Watanabe *et al.* 2007, Zgoła-Grześkowiak 2010). Generally, APs have been measured at lower concentrations in the surface water samples, where levels ranged from <LOD to 644 $\mu\text{g/l}$ for NP and from <LOD to 0.47 $\mu\text{g/l}$ for OP, respectively. However, in some samples the concentration levels were up to 200 $\mu\text{g/L}$ of APs due to pesticides loading commonly used for agriculture practice or loaded by industrial compounds (Navarro *et al.* 2010). According to Blackburn and Waldock (1995), some APs level measured in River Aire, were up to 180 $\mu\text{g/l}$, which exceeded *Daphnia* chronic effect levels and approach acute toxicity levels.

4.3 Sludge and sediment

4.3.1 Sludge

Each year, Sewage treatment plants in Europe produce 8×10^6 tons of sludge into the environment (Andreu *et al.* 2007). There are several research reports on the presence of APs and their ethoxylates in significant amount in sewage treatment plant (STP), as well as sewage and farmers' fields sludge (Andreu *et al.* 2007, Céspedes *et al.* 2008, Hawrelak *et al.* 1999, Lee *et al.* 1997, de Voogt *et al.* 1997). Besides industrial discharge and pesticide application, another significant source of APs in the environment is from the anaerobic breakdown of alkylphenol ethoxylates (APEs), mainly used as cleaning agent, emulsifier and wetting agents. Some APs, especially NP and OP, may be produced during wastewater treatment and transport, since anaerobic areas are common. Céspedes *et al.* (2008) reported substantial NP accumulation during the anaerobic sludge digestion in STP.

4.3.2 Sediment

The high log K_{OW} values of APs are indicative of their high hydrophobic nature which influences the environmental distribution of APs. Consequently, there is great tendency of APs to adsorb to the sediment in the environment. Sediment samples often show higher concentration of APs than aqueous samples (Bennie *et al.* 1997, Blackburn *et al.* 1999, Klosterhaus *et al.* 2013, Navarro-Ortega *et al.* 2010, Stuart *et al.* 2005). Ahel *et al.* (1994) found that the concentrations of APs in sediment are around 360 to 5100 times higher than APs' concentration in river water. Therefore, without testing concentration of APs in the associated sediment, just measuring the dissolved APs' concentration in the water samples can underestimate the total contamination of APs in the environment.

4.4 Aquatic biota

APs and BPA were generally detected at high concentrations among some aquatic biota, from non-detect to 1255 ng/g (Blackburn *et al.* 1999, Ferrara *et al.* 2005, Ferrara *et al.* 2008, Klosterhaus *et al.* 2013, Shao *et al.* 2007, Tsuda *et al.* 1999, 2000, Yang *et al.* 2013). A study in Italy found APs concentrations high in mullet, seabreams and shrimp rather than other seafood species, up to 1255 ng/g in shrimp sample collected from Fiumicino. (Ferrara *et al.* 2008). These higher concentrations of APs in mullets and shrimp may be due to the fact that these species had more interaction with the sediment where APs are likely to be associated than that for other fishes.

4.5 Food and human body

Due to the widespread occurrence of alkylphenolic compounds in the environment, humans may expose to these pollutants via several potential avenues such as air, water, food and beverage. APs and BPA were detected in typically food samples from grocery stores, as well as commercial milk, meat, baby food, beverage, bottle water and cereal (Diana and Dimitra 2011, Li *et al.* 2008, Lin *et al.* 2009, Niu *et al.* 2012, Rhind *et al.* 2007, Shao *et al.* 2005, 2007). The source of APs rather than BPA in food was not clear. Some scientists concluded that APs probably ends up in food products in a variety of ways such as exposure to pesticide and at different stages of food handling, packaging and processing procedure. The hydrophobic nature of APs, suggests that high concentration of APs will be found in high fat food samples. If the Biological Concentration Factor (Log BCF) value is bigger than 3, then the chemical is considered to exhibit a risk due to large bioaccumulation. According to Table 1, some APs are very lipophilic and resistant to biodegradation, so there is great potential for these compounds to accumulate in the tissue of animals in high trophic level. Tan and Mohd (2002) analyzed trace amount of APs in human umbilical cord blood, from non-detect to 15.17 ng/mL level.

5. Health effects of alkylphenolic compounds on humans and wildlife

The first evidence that alkylphenols could be estrogenic was published in 1938 by Dodds and Lawson (Dodds *et al.* 1938). Endocrine disruptors can disturb the hormonal system by mimicking the occurrence of natural hormones, blocking their production or by inhibiting or stimulating the endocrine system as illustrated in Fig. 2 (Soares *et al.* 2008). Healthcare information suggests that alkylphenols contaminants may relate to human endocrine disorders, problems with fertility, as well as brain and nervous system disease.

BPA is a widely known estrogenic endocrine disruptor, and hundreds of papers published in nearly decade have found that laboratory animals exposed to low levels (from LOD to 1431 ng/g) of it have promoted diabetes, mammary and prostate cancers, sperm count decreasing, reproductive problems, early puberty, obesity, and neurological problems (Staples *et al.* 2000). Certain alkylphenols are also considered to be a low-level endocrine disruptor. 17β -estradiol is the predominant natural estrogen form in female, which promotes the formation of female secondary sex characteristic, accelerate metabolism, maintenance as the maturation and function of accessory sex organs, as well as in the neuroendocrine and skeletal systems and is capable of promoting

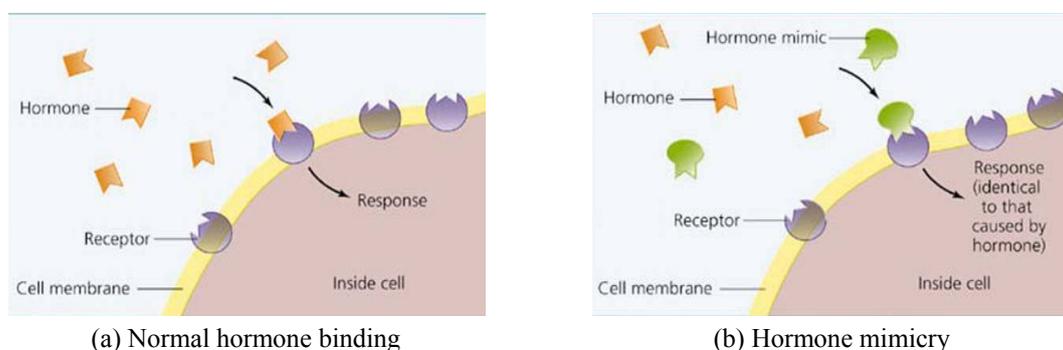


Fig. 2 Mechanism for hormone mimic of endocrine disruptors (Toxicology, <http://web.bryant.edu/>)

carcinogenicity in specific tissues. Nonylphenol was found to mimic the natural hormone 17β -estradiol by competing for the binding site of the oestrogen receptor (Lee and Lee 1996). Numerous tests (*in vitro* or *in vivo*) have been developed to estimate the influence of alkylphenols and BPA in triggering response from the endocrine system. For instance, nonylphenol was found capable as inducing the production of female protein in rainbow trout (*Oncorhynchus mykiss*) at 20.3 mg/L (Jobling *et al.* 1996), and mekada fish (*Oryzias latipes*) at 0.1 mg/L (Tabata *et al.* 2001). There are also numerous studies reported that BPA are able to affect the neonatal development of the reproductive organs by low dose exposure to female mice and rats. These evidences include chromosomal abnormalities in oocytes in females (Susiarjo *et al.* 2007), and long-term effects on accessory reproductive organs that are not observed until mid-life, such as uterine fibroids and paraovarian cysts (Newbold *et al.* 2007). BPA causes increase of prostate size (vom Saal *et al.* 1998), causes increase in prostate androgen receptors (Ritcher *et al.* 2007) and induces early stage prostate cancer (prostatic interepithelial neoplasia) (Ho *et al.* 2006) in rats and mice.

Currently, a dose of $50 \mu\text{g kg}^{-1} \text{d}^{-1}$ is considered to be 'safe' for daily human consumption by the US Environmental Protection Agency (EPA) and Food and Drug Administration (FDA). However, some researches indicate that a low dose of BPA showed acute and chronic effect in adult experimental animals: mice, rats and aquatic organisms. There is evidence showing that low dose of BPA ($\leq 50 \mu\text{g kg}^{-1} \text{d}^{-1}$) significantly stimulate the insulin secretion in mice (Ropero *et al.* 2008), significantly decrease daily sperm production in rats (Sakaue *et al.* 2001), affect the neuroendocrine system decreasing the maternal behavior in mice (Palanza *et al.* 2002) and disrupt the hippocampal synapses leading to the appearance of the senility in the brain as both rats and monkeys (Leranth *et al.* 2008, MacLusky *et al.* 2005). Ropero *et al.* (2008) confirmed that exposure of adult mice to a low oral dose of BPA ($10 \mu\text{g kg}^{-1} \text{d}^{-1}$) resulted in stimulation of insulin secretion which was mediated by estrogen receptor ($\text{ER}\alpha$), and then the prolonged high value of plasma insulin which induced insulin resistance and postprandial hyperinsulinaemia. From this result, some scientists implied that BPA may increase type 2 diabetes in many regions of the world (Alonso-Magdalena *et al.* 2005; 2008). Table 4 lists observed health effects of alkylphenols in experimental animals and the correlative effect to humans.

All these results demonstrate the fact that BPA and other alkylphenols are capable of disturbing the endocrine system and with various types of tissues and organs result in different modes of action. The effect of alkylphenols is very diverse and unpredictable because of the chemicals' ability to initiate numerous responses in living organisms.

6. Analytical techniques for the determination of alkylphenols

Great public concern about the occurrence and fate of APs in the environment and its effects on wildlife and human health had promoted the development of various analytical methods for the determination of APs in various matrices. Chromatographic techniques are the most important analytical method used for analyzing alkylphenolic compounds as presented in Table 3. Depended on the chemical nature, especially the volatility of the alkylphenol analytes, either gas chromatography (GC) or liquid chromatography (LC) is used. Gas chromatography is limited to NP, OP and other small APs molecules, unless derivatization step is introduced in the analytical procedure that allowed the determination of long-chain or polar APs. To avoid the problems associated with GC analysis, high-performance liquid chromatography (HPLC) has also been introduced for analysis of APs with various detection systems like UV and MS.

Table 4 The Health Effect of APs to Animals and Humans

Organism	Alkylphenols	Dose of effective	Effect	Human health trends	Reference
Rainbow trout	nonylphenol	20.3 mg kg ⁻¹ d ⁻¹	Female specific protein induction	Feminination, early sexual maturation	Jobling <i>et al.</i> 1996
Medaka fish	nonylphenol	0.1 mg kg ⁻¹ d ⁻¹	Vitellogenin induction		Tabata <i>et al.</i> 2001
Mice	BPA	20 µg kg ⁻¹ d ⁻¹	Abnormal oocyte chromosomes	miscarriage	Susiarjo <i>et al.</i> 2007
Mice	BPA	100 µg kg ⁻¹ d ⁻¹	Ovarian cysts/uterine fibroids	Polycystic ovary syndrome/uterine fibroids	Newbold <i>et al.</i> 2007
Mice	BPA and octylphenol	20 µg kg ⁻¹ d ⁻¹	Prostate hyperplasia	Prostate cancer increase	Vom Saal <i>et al.</i> 1998
Rats	BPA	10 µg kg ⁻¹ d ⁻¹	Prostate cancer		Ho <i>et al.</i> 2006
Mice	BPA	10 µg kg ⁻¹ d ⁻¹	Insulin resistance	Type 2 diabetes	Ropero <i>et al.</i> 2008
Rats	BPA	20 µg kg ⁻¹ d ⁻¹	Sperm count decrease	Sperm count decrease	Sakaue <i>et al.</i> 2001
Mice	BPA	10 µg kg ⁻¹ d ⁻¹	Decrease maternal behaviour	Cognitive function disorder	Palanza <i>et al.</i> 2002

6.1 Sample-preparation methods

Since the amount of APs in the environment occur at trace and even ultra-trace levels, it is necessary to build up a suitable sample-pretreatment techniques to eliminate potential matrix interferences, to isolate the target compounds and finally to enrich the sample extracts. Appropriate sample preparation procedures will significantly improve the selectivity and sensitivity of the analytical method. Collected water samples were often stored in the dark at 4°C and other type of samples below 0°C before extraction and analysis. The time between collection and extraction was as short as possible, usually within 48 hours. Recently, Guo *et al.* (2013) has examined the effect of storage time and temperature on the concentration of bisphenol A and phthalate in urine samples and estimated that the half-life of BPA in urine stored at 20°C was approximately 3 months, which is much longer than those reported for aquatic ecosystems.

6.1.1 Liquid-liquid extraction

Liquid-liquid extraction (LLE) is a conventional sample extraction method used to isolate APs from liquid matrices and followed by GC or LC determination. Since the efficiency and precision of the LLE technique is high, this technique is widely applied in the analysis of AP and other endocrine disrupting pollutants (Bennie *et al.* 1997, Diana and Dimitra 2011, Espejo *et al.* 2002, Klosterhaus *et al.* 2013, Tsuda *et al.* 2000, Zhu and Zuo 2013). The main disadvantages of LLE are relatively time consuming and the use of large volumes of organic solvents that are usually toxic and very expensive. In recent years there is an increasing tendency to replace LLE by solid-phase extraction (SPE). However, APs are commonly bio-accumulated in the fatty tissue in

biota samples. Some biota samples form a very fine emulsion during sample pretreatment, which is very tedious to filter and easily clogs the SPE cartridge (Ferrara *et al.* 2008). LLE technique is therefore still preferred technique in most analytical processes for biota samples. Several papers have described the application of LLE for extraction of APs from lipids or fatty tissues (Meier *et al.* 2005, Mottaleb *et al.* 2009, Zhu and Zuo, 2013).

6.1.2 Solid phase extraction

Developed in 1980s, solid phase extraction is considered as a powerful technique for chemical isolation and purification. Several kinds of SPE cartridges have been successfully applied for the extraction and preconcentration of APs. The sorbents employed in SPE of APs can be divided to three basic types: silica-based, polymer-based (essentially Oasis HLB) and carbon-based. Non-polar reverse-phase (RP) sorbents (C_2 , C_8 , C_{18}) with the silica-base cartridge are the most widely used sorbents in APs compounds extraction (Andreu *et al.* 2007, Blackburn *et al.* 1995, Chen *et al.* 2006, Dévier *et al.* 2013, Koh *et al.* 2008, Isobe *et al.* 2001, Sole *et al.* 2000). The extraction is mainly based on non-polar Van der Waals interactions between the analytes and the sorbent. Recently, several new hydrophilic polymeric (Oasis HLB cartridges) sorbents have also been employed to obtain better recoveries for polar AP compounds (Jahnke *et al.* 2004, Sánchez-Avila *et al.* 2009, Shao *et al.* 2005).

6.1.3 Other sample extraction techniques

Ultrasonic extraction has recently become to be an attractive method in sample pretreatment (Blackburn *et al.* 1999, Niu *et al.* 2012, Zuo *et al.* 2004, Jiao and Zuo 2009). The application of ultrasonic wave increases extraction efficiency, shortens extraction time and reduces organic solvent consumption. Many other advanced sample extraction approaches such as steam distillation extraction (Li *et al.* 2008), solid-phase microextraction (SPME) (Pan and Tsai 2008), liquid-phase microextraction (LPME) (Yang *et al.* 2013), accelerated solvent extraction (ASE) (Andreu *et al.* 2007, Céspedes *et al.* 2008, Fiedler *et al.* 2007, Navarro-Ortega *et al.* 2010, Shao *et al.* 2007, Wang *et al.* 2009), soxhlet extraction (Blackburn *et al.* 1999, de voogt *et al.* 1997, Hawrelak *et al.* 1999), Microwave-assisted extraction (MAE) (Biggers and Laufer 2004, Laufer *et al.* 2005), supercritical-fluid extraction (SFE) (Lee *et al.* 1997), stir bar sorptive extraction (SBSE) (Baltussen *et al.* 1999), membrane assisted solvent extraction (Salgueiro-González *et al.* 2013) and Dispersive liquid-liquid microextraction (Zgoła-Grześkowiak 2010) have also been reported for the extraction and enrichment process in APs analysis.

6.2 Instrumental analysis

6.2.1 Gas chromatography

GC plays a key role in separation of sufficiently volatile organic compounds in environmental samples. Nowadays, capillary GC has been considered as the most important and widely used instrument in the analysis of various alkylphenols and their derivatives in air, water, soils, sediments and biota matrices. (Berkner *et al.* 2004, Blackburn *et al.* 1999, Blackburn and Waldock 1995, Chen *et al.* 2006, Diana and Dimitra 2011, Espejo *et al.* 2002, Ferrara *et al.* 2005, Isobe *et al.* 2001, Sánchez-Avila *et al.* 2009, Jonsson *et al.* 2008, Lin *et al.* 2009, Meier *et al.* 2005, Mottaleb *et al.* 2009, Rhind *et al.* 2007, Tsuda *et al.* 1999, 2000, Zhang and Zuo 2005, Zuo *et al.* 2007, Zhu and Zuo 2013).

Gas chromatography is commonly acknowledged as a more powerful separation technique than HPLC (Thiele *et al.* 1997). When combined with mass spectrometry, GC/MS can provide basic

information for both reliable identification and quantitation of alkylphenolic analytes (Ying *et al.* 2002, Zhu and Zuo 2013). During the past decade, many published works have employed this technique for alkylphenols analysis (Ferrara *et al.* 2005, 2008, Meier *et al.* 2005, Mottaleb *et al.* 2009, Navarro-Ortega *et al.* 2010, Wang *et al.* 2009). However, most methods available were focused on only one or two classes of alkylphenols (Ying *et al.* 2002). Recently, great efforts have been made to develop generic methods that allow simultaneous determination of a broad range of alkylphenolic compounds (Navarro *et al.* 2010, Sánchez-Avila *et al.* 2009).

Most alkylphenols (APs), and alkylphenol ethoxylates (APEs) with fewer than four ethoxy groups are small molecules and can be directly determined by gas chromatography (Blackburn *et al.* 1999, Blackburn and Waldock 1995, Chen *et al.* 2006, Espejo *et al.* 2002, Isobe *et al.* 2001, Lin *et al.* 2009, Li *et al.* 2008, Mottaleb *et al.* 2009, Rhind *et al.* 2007). However, the presence of hydroxyl groups in alkylphenols, requires modification of this polar functional group to improve their chromatographic behavior. Hence, the derivatisation procedure is commonly adopted in many analytical methodologies for better peak shape and resolution (Bennie *et al.* 1997, Hawrelak *et al.* 1999, Kawaguchi *et al.* 2005, Xie *et al.* 2006). Silylation of APs with BSTFA/TMCS (Ballesteros *et al.*, 2006), MTBSTFA/TBDMCS (Pan and Tsai 2008) or pentafluorobenzoyl chloride (PFBCl) (Boitsov *et al.*, 2004) and Acylation of APs with acetic anhydride (Nakamura *et al.* 2004) or TFAA (Ferrara *et al.* 2008) were all reported in the literature.

For the analysis of alkylphenols, bisphenol A and their chlorinated derivatives in waste water, Ballesteros *et al.* (2006) have successfully applied GC with a MS in the electron impact ionization (EI) mode. Quantitation was performed by addition of bisphenol F (BPF) as internal standard to the extracts in the derivatization procedure prior to the GC determination. Quantification limits ranged between 20 ng/L and 400 ng/L. Sánchez-Avila *et al.* (2008) determined NP, OP, NP1E (Nonylphenol monoethoxilathed), NP2E (Nonylphenol diethoxilathed) and BPA in industrial sewage samples by GC/MS in the selected ion monitoring (SIM) mode for sensitive detection (18.0-166 ng/kg sewage) and selective identification. The internal standard anthracene was added to the original samples to correct for nonquantitative recoveries during extraction. Espejo *et al.* (2002) used LC-ESI-MS and GC-EI-MS to examine 18 isomeric 4-nonylphenol and 4-tert-octylphenol in municipal sewage wastewater. Espejo *et al.* (2002) also determined the percentage composition of isomeric 4-nonylphenols by using GC-FID instrument to quantify each isomer. The GC-EI-MS was used to identify each isomer according to the corresponding mass spectra. Generally, electron impact ion source mass spectrometry (EI-MS) is widely used for providing characteristic fragmentation mass spectral pattern to confirm the identification of various alkylphenolic compounds.

Negative chemical ionization mass spectrometry (NCI-MS) is also reported to be a suitable method for the selective identification of alkylphenol compounds in environmental matrices (Meier *et al.* 2005). Boitsov *et al.* (2004) reported that derivatization of APs and APEs with pentafluorobenzoyl chloride (PFBCl) will provide derivatives with high electron affinities that can be specifically and sensitively analyzed by GC-NCI-MS.

6.2.2 Liquid chromatography

Liquid chromatography (LC) has also been proven to be a sensitive and reliable technique for most environmental contaminants analysis, especially for alkylphenol ethoxylate (APEs) (non-ionic surfactants that are precursors of alkylphenols in the environment). Due to its high sensitivity and suitability for separating nonvolatile or thermally fragile species, LC/MS has been gaining popularity for alkylphenol analysis during recent years (Andreu *et al.* 2007, Céspedes *et*

al. 2008, Cantero *et al.* 2006, Dévier *et al.* 2013, Sole *et al.* 2000). However, the LC does not provide enough resolution for complicated environmental samples based on the lower total theoretical plates and less compatibility to mass spectrometry compared to GC. In recent years, it has become feasible to couple two or more mass analyzers to form tandem mass spectrometers. LC/MS/MS is gradually being used for alkylphenol analysis because of its higher resolution, selectivity and sensitivity (Céspedes *et al.* 2008, Jahnke *et al.* 2004, Niu *et al.* 2012, Koh *et al.* 2008, Tsuda *et al.* 1999, Salgueiro-González *et al.* 2013, Shao *et al.* 2005, 2007).

7. Conclusions

This paper provided an overview on the environmental presence, fate, and health effects of bisphenol A and other alkylphenols as well as the analytical methods for determination of alkylphenols in various environmental matrices. In general, APs are hydrophobic and have relatively high coefficient for adsorption onto soil and sediments, and for bioaccumulation into lipids of organisms in the environment. Extensive animal exposure experiments have shown that alkylphenols, as a kind of environmental endocrine disruptors, have impact on the health of human and wildlife through interaction with hormone systems. To date, numerous analytical methods have been developed to detect APs in the environment. GC-MS has been remained as a choice of AP analytical techniques. Various sample pretreatment, extraction, purification and instrumental analysis procedure have been also reviewed and compared for their advantages and disadvantages depended on the type of samples such as air, surface water, sediment, soil and biota.

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