



# Review on the determination and distribution patterns of a widespread contaminant artificial sweetener in the environment

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## Abstract

The accurate determination of widespread artificial sweeteners (ASs) and the information of their distributions in environments are of significance to investigate the environmental behaviors. This paper firstly reviews the typical analytic methodologies for ASs and the main influencing factors during the analytic processes. Solid-phase extraction (SPE) with LC-ESI-MS is currently the leading-edge method. However, the efficiency and accuracy for ASs analysis in environmental samples are also dependent on the SPE cartridges, buffers and pH, matrix effects, and sample stability. A basic procedure for ASs determination in different environmental samples is proposed. The current occurrences of ASs in environments are then evaluated. The ASs, especially the acesulfame and sucralose, are widely detected in various environmental medium. The concentrations of investigated ASs are generally in the order of wastewater treatment plants (WWTPs) influent > WWTPs effluent > surface water > groundwater > drinking water; and atmosphere > soil. The ASs levels in the environment exhibit significant differences among different regions. Further analysis indicates that the phenomenon is highly correlated with the consumption patterns and the removal efficiency of WWTPs in a specific country.

**Keywords** Artificial sweeteners (ASs) · Solid-phase extraction (SPE) · LC-ESI-MS · Concentrations · Consumption patterns · Removal efficiency

## Introduction

Artificial sweeteners (ASs), commonly known as sugar substitutes, are featured for their high-intensity sweetness but with no or insignificant energy. Since ASs are generally not metabolized as carbohydrates, no glycemic effect/insulin response or calorie intake would be caused and are thereby considered to be safe to human health with acceptable daily intake (ADI)

(Brusick et al. 2010; Viberg and Fredriksson 2011). Therefore, ASs have been widely used in various industries with large consumption, such as food, soft drinks, drugs, and animal feeds (Kroger et al. 2006; Subedi and Kannan 2014). The most popular ASs include acesulfame (ACE), sucralose (SUC), saccharin (SAC), cyclamate (CYC), aspartame (ASP), neotame (NEO), and neohesperidin dihydrochalcone (NHDC). Their main physiochemical characteristics of ASs are shown in Table 1 (Lange et al. 2012). It is noted that the global market for ASs exceed over \$5.1 billion, of which the USA and Europe currently account for 65% (Bennett 2008). Asia-Pacific is one of the main regions for ASs production, which occupies over 50% of the world production. The total output of ASs grow approximately 10% between 2009 and 2010, reaching approximately 109,000 tonnes. Among them, China is the biggest country in ASs consumption as well as production. The national total production of ASs exceeds 80,000 tonnes (Chen et al. 2012).

ASs are highly soluble and easily transferred among different media but eventually reside in the receiving environmental bodies (Houtman 2010). In contrast to other trace contaminants, such as pharmaceuticals and personal care products,

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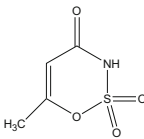
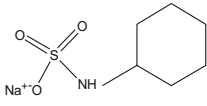
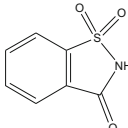
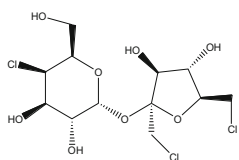
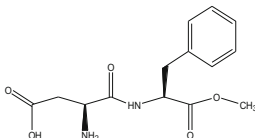
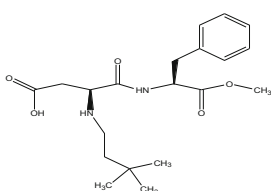
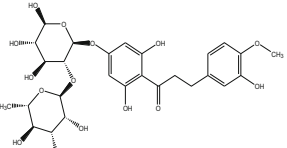
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**Table 1** Main physicochemical properties of the typical ASs (Lange et al. 2012; Feng et al. 2013)

Catagory	Structure	MW <sup>a</sup> (g/mol)	lgK <sub>ow</sub>	Sugar equivalence <sup>b</sup>	ADI <sup>c</sup>	Main Market
ACE		163.2	-1.33	200	9	North America, Europe and Asia
CYC		179.2 (202.2)	-1.61	30	7	Europe and Asia
SAC		183.2	-0.91	300	5	American, Europe and Asia
SUC		397.6	-1	600	17	North America,
ASP		294.3	0.07	610-220	40	North America, Europe and Asia
NEO		378.5	2.39	7000-1 3000	2	America
NHDC		612.6	0.75	1800	5	Europe and Japan

<sup>a</sup> MW molecular weight

<sup>b</sup> Sucrose = 1 (relative to a 10% sucrose solution). Different numbers indicate effect in different foods

<sup>c</sup> ADI acceptable daily intake (mg/kg (body weight) day)

the available information on the environmental distribution of ASs is far more limited despite their early market entry. The ASs studies have been gradually increasing since 2007, when Sweden firstly reported the existence of SUC in wastewater treatment plants (WWTPs) and surface waters (Brorströmlundén et al. 2008). So far, various ASs have been identified in different environmental matrices (Buerge et al. 2011; Mead et al. 2009; Oppenheimer et al. 2011; Scheurer et al. 2009; Subedi and Kannan 2014).

The potential risks of ASs to natural environments can not be ignored due to the enormous consumption, large release and wide occurrence in environment. Though the ASs are chemically designed as sugar substitutes and are commonly considered safe with ADI amounts, the discussions on ASs ecotoxicity is debatable based on different assessment criteria in various environments. In fact, increasing studies have recently warned of the potential environmental risks of ASs (Amy-Sagers et al. 2017; Bian et al. 2017; Calza et al. 2013; Lin et al. 2015;

Oliveira et al. 2017; Ren et al. 2016; Wiklund et al. 2012; Praveena et al. 2019). For example, a study on crustaceans showed that physiology and locomotive behavior was affected by exposing to SUC at the environmentally relevant concentrations of 0.5–500 µg/L. SUC may also induce sublethal effects to *Daphnids* neurological and oxidative alterations at the concentration range of 0.0001–5 mg/L (Wiklund et al. 2012). Moreover, SUC was found to affect the lipid peroxidation, hydroperoxide and protein carbonyl contents, and the activities of antioxidant enzymes of *Cyprinus carpio* at environmentally relevant concentrations (0.05 and 155 µg/L) with different exposure times (12, 24, 48, 72, and 96 h) (Saucedo-Vence et al. 2017). In addition, ASs are likely to transform into new products via various pathways which may exhibit higher toxicity than the parent compounds. Sang et al. measured the acute toxicity of ACE metabolites (with photo treatment) to *V. fischeri* and demonstrated that the biotoxicity of ACE metabolites was significantly amplified to  $EC_{50} = 125.5$  mg/L with a measurable magnification factor of 575 compared with the parent compound (Sang et al. 2014). Results showed that the potential ecological impacts of ASs at environmental level would be increased via such amplifying effects. However, the public is currently having quite limited knowledge of the ASs pollution and the potential ecological risks though they are frequently applied in our daily life. Obviously, the accurate determination of ASs and the information of their distribution in the environment are of significant importance for better understanding the ASs as well as their potential ecological impacts.

Therefore, the main aim of this paper is to (1) compile the currently available analytical methodologies and main influencing factors for the ASs determination to provide guidance for the accurate analysis in environmental mediums; (2) illustrate the current occurrences of typical ASs in the natural environments to give an insight of the ASs contamination; (3) analyze the main reasons for the ASs-specific distribution patterns around the world.

## Determination of ASs and the key influencing factors

Numerous techniques have been developed for ASs analysis (Table 2). However, the efficiency and feasibility of these reported methods vary greatly for ASs detection. The procedures of GC-MS and HPTLC-MS are complicated and ineffective for the determination of some specific ASs (such as SUC), which made them hard to analyze the multianalytes of ASs in environmental samples (Mead et al. 2009; Morlock et al. 2011). The newly proposed FT-Raman spectroscopy and capillary electrophoresis are also questioned by the limited efficiency and accuracy which requires further verification for future application (Duarte et al. 2017; Stojkovic et al. 2013).

LC-MS is currently the most widely used methodology for ASs analysis due to its multianalytes determination capability and evident superiority in both sensitivity and selectivity. Therefore, LC-MS is applied for ASs detection from low concentration samples with complex matrices, such as wastewater influents and sludge (Loos et al. 2009; Mawhinney et al. 2011; Neset et al. 2010; Oppenheimer et al. 2011). Considering its high sensitivity, the ultra-performance liquid chromatography tandem mass spectrometry may be a good option (Table 2). However, the operational costs should be also considered (Perkola and Sainio 2014). LC-MS is generally equipped with an electrospray interface (ESI) for the ionization of ASs which is further divided into positive and negative ionization modes. However, the positive ionization mode is only suitable for the determination of ASP, SAC, and SUC though it may show higher sensitivity and more fragmentation information over negative ionization, which limits its application (Ferrer and Thurman 2010; Minten et al. 2011). So far, LC-MS with negative ionization mode is the only feasible method to simultaneously determine all popular ASs (Kokotou et al. 2012; Lange et al. 2012).

## Limit of detection (LOD)

The concentration of ASs in environmental samples is generally low, which ranges from ng/L to µg/L depending on the specific AS and different environmental samples (Berset and Ochsenbein 2012; Ordonez et al. 2013). The limit of detection (LOD) of ASs varies greatly with different analytic methods from different samples (Table 2). In order to detect the trace ASs in the environment, the LOD should be considered in choosing the optimal analytic instruments. For example, the capillary electrophoresis is not suitable for the analysis of ASs in environmental samples considering its LOD. Generally, the LOD of LC-MS analysis meets the detection requirements for most of the ASs. However, it should be noted that the SUC has a much lower response than other ASs due to the hydroxyl group (Loos et al. 2009). For example, the detection limit for SAC, ACE, CYC, ASP, and NHDC are respectively 500, 5, 50, 100, and 130 ng/L, but it is 2500 ng/L for SUC with the LC-MS analysis (Tran et al. 2014). It would increase the analytic difficulty for the trace SUC in environments.

Generally, there are two major strategies to further promote the detection performances of ASs. The simplest way to enhance the sensitivity of determined ASs is to add extra basic buffer solutions. For example, tris-(hydroxymethyl)-aminomethane is reported to increase the signal response from 30% for NHDC to 290% for SAC by improving the deprotonation of targeted analytes by LC-MS. The LOD is thereby improved to be respectively 1 ng/L for NEO, 2 ng/L for ACE and SAC, 5 ng/L for CYC and ASP, and 10 ng/L for SUC and NHDC (Scheurer et al. 2009). But the

**Table 2** Analytical instruments for the ASs determination

Instrumental	Targeted ASs	Detection limit (ng/L)	Reference
Liquid chromatography tandem mass spectrometry (LC-MS)	SUC, SAC, CYC, ASP, ACE, NEO, NHDC	SUC: 2500; SAC: 500; ACE:5; CYC:50; ASP:100; NHDC: 130	(Tran et al. 2014)
High-performance liquid chromatography (Triple Quadrupole) mass spectrometry (HPLC-MS)	SUC, SAC, CYC, ASP, ACE, NEO, NHDC	10	(Berset and Ochsenbein 2012; Ordonez et al. 2013)
Ultra-performance liquid chromatography tandem (electrospray ionization) mass spectrometry	SUC, SAC, CYC, ACE	SUC: 20; SAC:4; ACE:2; CYC:1	(Perkola and Sainio 2014)
Ultra-performance liquid chromatography coupled to a quadrupole-time-of-flight mass spectrometer	SUC	10	(Gagofferrero et al. 2017)
Liquid chromatography (electrospray ionization) with high-resolution mass spectrometry	SUC	100 (effluent); 50 (surface water); 10 (drinking water)	(Neset et al. 2010)
Reversed-phase liquid chromatography (electrospray ionization) mass spectrometry	SUC	10	(Loos et al. 2009)
Gas chromatography with mass spectrometry (GC-MS)	SUC	100	(Mead et al. 2009)
High-performance thin-layer chromatography with mass spectrometry (HPTLC-MS)	SUC	100	(Morlock et al. 2011)
Capillary electrophoresis with contactless conductivity detection	ASP, CYC, SAC, ACE	mg/L level	(Stojkovic et al. 2013)
Ion chromatography with mass spectrometry (IC-MS)	ACE, SUC, SAC, CYC	ACE:8; SUC: 5000; SAC:21; CYC:3	(Robertson et al. 2016; Roy et al. 2014; Van Stempvoort et al. 2011)
FT-Raman spectroscopy	ASP, CYC, SAC, ACS	—	(Duarte et al. 2017)

enhancing effects by sole solvents addition in post columns would be limited. On one hand, the buffer concentration must be strictly controlled to avoid the unnecessary contamination of the mass spectrometer interface (Scheurer et al. 2009). On the other hand, the low concentration of ASs and potential interferences in environmental samples also exhibit great obstacles for those trace ASs detection. Another efficient and applicable approach to detect the trace ASs is to pre-concentrate the environmental samples. The traditional strategy of pre-concentrating trace compounds is through solid-phase extraction (SPE) by loading high volumes of sample onto the SPE cartridge. For example, the typical volumes for off-line SPE are 200–1000 mL for water analysis (Loos et al. 2009), and 50–200 mL for wastewater analysis (Scheurer et al. 2009). The sorbed ASs are then eluted with low volumes of optimal eluents and further concentrated by evaporation before LC-MS analysis (Calza et al. 2013; Oppenheimer et al. 2011; Saucedo-Vence et al. 2017; Wiklund et al. 2012). Therefore, the pre-concentration factors for ASs could be up to 1000 times (Kokotou et al. 2012), which is quite suitable to detect those trace ASs with low responses in environmental samples. However, the drawback of SPE lies in its relatively more complicated procedures and the recovery efficiency is also influenced by various factors, such as the selection of SPE cartridges, eluents, etc. Besides, the desiring chromatography is important for the simultaneous determination of various ASs in one sample. Some of the ASs may exhibit similar polarity that is hard to separate. The optimization and validation of analytic conditions (such as the mobile phase, chromatographic columns and analytic procedures of LC, and the parameters of MS ( declustering potential, collision energy, and cell exit potential)) are necessary and helpful to obtain adequate separation and get optimal sensitivity of ASs (Scheurer et al. 2009)

### Selection of optimal SPE cartridges

To effectively concentrate the ASs, the selection of suitable SPE cartridges is extremely important but difficult due to the specific characteristics of particular ASs. Currently, numerous categories of commercial SPE have been developed. The SPE sorbents employed for ASs analysis are commonly silica- or polymer-based and modified with hydrophobic or/and hydrophilic moieties to provide either reversed-phase or both reversed-phase and ion-exchange functionality according to the wide ranges of ASs polarities. Their efficiencies for ASs recovery have been extensively tested but no consistent conclusions were obtained.

Scheurer et al. concluded that the polymeric-based cartridges could exhibit better performance in ASs recovery after evaluating 10 different cartridges. The recovery efficiency

ranged from 56% for NHDC to 96% for NEO with Bakerbond SPE<sup>TM</sup>SDB-1 cartridge (polymeric-based) (Scheurer et al. 2009). Recently, Gan et al. suggested the application of polymeric-based Poly-Sery PWAX cartridge in recovering the ASs from environmental samples by comparing ten different cartridges. The recoveries could range from 77 to 99% in all the seven tested ASs (Gan et al. 2013b). However, Zygler et al. considered that the silica-based cartridges were more beneficial for the recovery of multianalytes as the polymeric ones were sometimes inefficient to recover specific AS (Zygler et al. 2010). But they also admitted that the ASs recovery efficiencies were highly correlated with sorbent characteristics of cartridges (e.g., structure, porosity, particle diameter, carbon load, surface area) (Zygler et al. 2010). Better recoveries are commonly directly related to larger surface area and carbon load. For example, the recoveries of ACE and CYC were low (74 and 41%, respectively) by the Oasis HLB filled with only 60 mg of sorbent. But it showed quantitative recovery of all sweeteners with increasing sorbent fillings (300 mg) (Zygler et al. 2010).

Moreover, the types of eluents and pH exhibit remarkable influences on the ASs recovery by SPE cartridges. The traditional eluent is a mixture of methanol (MeOH) and water. However, the minor modification of buffers and pH may improve the recovery efficiency greatly. For instances, Zygler et al. found that Bakerbond SPE Octadecyl and Zorbax C18 cartridges presented very low recoveries for ACE and ASP for all tested buffer compositions, but it increased to 92% for the targeted pollutants with the use of formic acid/N,N-diisopropylethylamine buffer (Zygler et al. 2010). Gan et al. obtained satisfactory recoveries for all the detected ASs (SUC, ACE, SAC, NADH, CYC, NEO, and ASP) by modifying the wash buffer with 25 mM sodium acetate solution and MeOH containing 1 mM tris (hydroxymethyl) aminomethane as eluents when employing the Poly-Sery PWAX cartridge (Gan et al. 2013b). As to the pH, Ordóñez et al. obtained good trueness and recovery of 73–112% of six ASs (SUC, ACE, SAC, NADH, CYC, and ASP) with Oasis HLB cartridge by adjusting the pH to 2 (Ordóñez et al. 2012). But Loos et al. thought that the extraction for SUC with Oasis HLB was much more efficient at neutral pH and a recovery of  $62 \pm 9\%$  could be achieved (Loos et al. 2009).

Overall, it can be concluded from the above discussions that it is difficult to get desiring recoveries for all the ASs compounds by employing one specific SPE cartridge. The recovery efficiency of ASs depends on numerous factors, such as the particular physicochemical properties of ASs, suitable SPE cartridge, optimized eluents and pH, and even the different samples (Ordóñez et al. 2013). In order to obtain high accuracy of ASs determination, the optimal SPE cartridges, as well as eluents and pHs, should be tailored for the particular investigated ASs and treated samples with extensive experiments.

## Matrix effects

“Matrix effects” refers to the negative effects of the non-targeted compounds in samples on the analysis of targeted analytes, which is mainly presented by suppressing or augmenting the signal response during LC-ESI-MS analysis (Oppenheimer et al. 2011; Scheurer et al. 2010). A correlation of high concentration of dissolved organic matter with the low recovery of SUC was found by Mead et al. (Mead et al. 2009). However, the environmental samples are usually mixtures of various compounds. Though the pre-concentration and cleanup procedures by SPE cartridges could remove part of the interfering compounds, some of the matrix components, especially those possessing similar properties of targeted analytes, could also co-elute and concentrate during the process. In fact, the matrix effect is more significant in highly pre-concentrated samples. It has been reported that severe matrix effects were induced by ESI in analyzing the wastewater samples due to the high concentration of interfering compounds (Adams et al. 1994; Buerge et al. 2011; Minten et al. 2011; Oppenheimer et al. 2011). Scheurer et al. demonstrated that the recoveries of ACE, CYC, SAC, and SUC from different environmental samples were in the order of drinking water (76–95%) > surface water (52–96%) > wastewater (23–50%) (Scheurer et al. 2009). Therefore, in order to get desirable results, the matrix effects for ASs detection should be assessed and optimized carefully. Principally, wastewater samples are not suggested to pre-concentrate as extensively as drinking water.

Nowadays, in order to effectively compensate for the interferences of matrix compounds, the internal isotopically labeled standardization during the sample preparation is used as a common strategy. It has been proven to get better quantification precision than that of external calibration and is generally mandatory for quantification correction for ASs determination in environmental samples (Buerge et al. 2011; Gan et al. 2013b; Loos et al. 2009; Oppenheimer et al. 2011). The accuracy of SUC quantification was evidently improved with the spiked SUC  $d_6$  as deuterated internal standard (IS) (Loos et al. 2009). The main ISs include SUC- $d_6$ , ACE- $d_4$ , CYC- $d_{11}$ , NEO- $d_3$ , NEO- $d_5$ , NHDC- $d_3$ , and ASP- $d_5$  (Buerge et al. 2011; Gan et al. 2013b; Loos et al. 2009; Oppenheimer et al. 2011). But SUC- $d_6$  is currently the most applied one which might attribute to its wide occurrence in environments but low response during instrumental analysis.  $^{13}\text{C}$  labeled-compounds are also potential ISs and a better performance is expected as the  $^{12}\text{C}$  and  $^{13}\text{C}$  exhibit less differences in physical properties than  $^1\text{H}$  and  $^2\text{H}$ . However, the high cost limits its application for the analysis of environmental samples. So far, SAC- $^{13}\text{C}_6$  is the only  $^{13}\text{C}$ -labeled AS that has been used for ASs analysis in environmental samples.



## ASs extraction from real environmental samples

ASs are generally compartmented in various environmental medium. The extraction procedures vary in different samples (Table 3). Thus, in this study, the commonly used approaches to extract AS from different environmental samples are also concluded.

## ASs extraction from water-phase samples

The extraction of ASs in water-phase samples is relatively simple. The collected samples firstly filtrate through 0.45  $\mu\text{m}$  cellulose nitrate membrane to remove the suspended particulate matters and are then frozen immediately on dry ice. The stabilization agents are commonly recommended to better maintain the stability of ASs and the analysis should be completed shortly. The determination of targeted ASs could be simply conducted by centrifuging and transferring the supernatant into amber auto-sampler vials directly with the spike of MeOH and IS mixture (matrix effects correction) before LC-ESI-MS analysis. A satisfactory recovery has been reported for ACE, CYC, SAC, and SUC (ranging from 120 to 135%) (Tran et al. 2015; Tran et al. 2013). The pre-concentration and cleanup procedure is frequently required to remove the impurities and meet the LOD of instruments as the concentrations of ASs in wastewater are usually quite low. The large application of commercial SPE cartridges could help to achieve this goal with good recoveries ( $100 \pm 35\%$ ) (Gan et al. 2013a; Ma et al. 2017; Ngoc Han et al. 2015; Ordóñez et al. 2012; Subedi et al. 2014).

## ASs extraction from solid-phase samples

The extraction of ASs from solid-phase samples (e.g., sludge, soil, plants, fermented compost, fish) would be more complicated due to the potential interferences, such as the sorption and entrap by particulates.

For quantification of targeted ASs in the suspended solids or activated sludge, the simplest way is to collect them from wastewater samples using syringe filtration. The filter tip should further be eluted with MeOH to rinse the possible residues. Then, the extract is spiked with IS mixture, dried under gentle streams of nitrogen, and re-dissolved in MeOH/H<sub>2</sub>O solution before analyses. The recovery efficiency is reported to maintain at 83–109% for ACE, CYC, SAC, and SUC in activated sludge (Ngoc Han et al. 2015). But in a more scientific way, the hydrophilic ASs in solid samples should firstly be freeze-dried. Then, the freeze-dried solids are spiked with a mixture of corresponding ISs and extracted with suitable solvents by sonication or Soxhlet extraction (Gan et al.

2014; Ma et al. 2017). ASs extractions from solid samples could also be conducted by pressurized liquid extraction. The obtained extracts are further concentrated with SPE cartridges. Satisfactory recoveries can be obtained for all the ASs ranging from 94 to 116% for ACE, CYC, SAC, ASP, NHDC, and SUC by adopting this approach (Ordóñez et al. 2013). However, the procedures and operating conditions are complicated and strict, which require suitable temperature, buffer solutions, pH, static extraction time, number of cycles, etc. Also, special instruments are required and thus limit the large application. The extracts are further purified and concentrated via SPE cartridges before analysis. As shown in Table 2, the main principals and steps for the ASs extraction from environmental samples are similar, except the different extraction solvents, eluents, etc. A basic procedure is therefore concluded to provide certain guidance for the recovery of ASs from different samples (Fig. 1). However, it should be noted that validation tests are required to confirm the efficiency of methods (Scheurer et al. 2009).

## Sample stability

The importance of sample stability for the accurate determination of ASs in environmental samples is greatly underestimated considering the possible microbial degradation. Until now, the available data on this part is currently limited. Van Stempvoort et al. once found that the ACE and SUC kept stable in groundwater samples after long storage in both refrigerator and frozen state (Van Stempvoort et al. 2011; Van Van Stempvoort et al. 2011a). The result is understandable as the ACE and SUC are well-known for their persistence in environment and are deemed as good wastewater-associated indicators (Buerge et al. 2009; Soh et al. 2011; Yang et al. 2017). However, significant losses were observed for SAC and CYC in both refrigerated wastewater and groundwater samples after 3 weeks. They were even near to 100% loss after 1 year in refrigerating storage for groundwater samples. Besides, Lang et al. indicated that ACE, CYC, SAC, and SUC could keep stable for 3 weeks in wastewater-influenced surface water when refrigerating. But the stability of ASP only maintained for 1 week (recoveries below 11%) even with acidic treatment (Lange et al. 2012).

The above discussions indicate that the long-term refrigerating storage is not suitable for the accurate determination of the non-persistent ASs even though the samples had been filtered. The potential microbial degradation seems to be impossible to avoid. The requirement for quality assurance in the processes of sampling and shipping before analysis is imperative. Otherwise the efforts of applying expensive and modern instruments for trace ASs analysis would be in vain. Lange et al. provided an insight of utilizing the easy approach (HCl addition) to shortly stabilize the environmental ASs samples

**Table 3** ASs extraction procedures from environmental samples

Environmental samples	Main procedures	Solvents	Recovery efficiency	Reference
Water-phase samples	Syringe filtration; spiked with IS mixture before analysis	MeOH	120 to 135% for ACE, CYC, SAC, and SUC	(Iran et al. 2015; Tran et al. 2013)
Water-phase samples	Syringe filtration; concentrated and purified with SPE cartridges; spiked with IS mixture before analysis	Wash buffer: sodium acetate solution (pH 4); Eluent: MeOH containing 1 mM TRIS MeOH/H <sub>2</sub> O	77–99% for ACE, NEO, NHDC, ASP, CYC, SAC, and SUC	(Gan et al. 2013b)
Activated sludge	Syringe filtration; spiked with IS mixture and dried with nitrogen; and finally, re-dissolved in solvents before analyses	MeOH/H <sub>2</sub> O	83–109% for ACE, CYC, SAC, and SUC	(Ngoc Han et al. 2015)
Activated sludge	Samples freeze-dried, spiked with ISs and equilibrated; Vortex-mixed and extracted with solvents by ultrasonication twice; concentrated the extracts and purified by cartridges before analyses	Extraction: methanol/water mixture (5:3 v/v); Eluent: MeOH; mixture of acetone, MeOH, and ethyl acetate (2:2:1 v/v/v); and MeOH containing 5% ammonia	68 ± 13% for ACE, ASP, SAC, and SUC	(Subedi and Kamnan 2014)
Solids samples (soil, manure, dust, plant, etc.)	Samples freeze-dried, grounded, and sieved through 0.2-mm stainless mesh; spiked with ISs; samples (minimum 0.01 g for feed, 0.1 g for manure, 0.1 g for plant, and 1.0 g for soil) were extracted with extraction solvents by shaking for 20 min for twice; concentrated the extracts and purified by cartridges before analyses	Extraction: 10 mM HAc/NaAc buffer (pH 4); Eluents: 25 mM HAc/NaAc buffer (pH 4) and MeOH containing 1 mmol/L TRIS and 5% NH <sub>3</sub> ·H <sub>2</sub> O (v/v) at pH 11.	82–96% for ACE, NEO, NHDC, CYC, SAC, and SUC, but only 39% and 42% for ASP in soil and dust, respectively	(Gan et al. 2014; Ma et al. 2017)
Algae and daphnid	Sonicated the samples with solvents at 60 °C for 30 min (twice); combined the extracts and evaporate the acetone before analysis	Extraction solvents: MeOH/acetone (1:9) with phenyl β-D-glucopyranoside as IS	112 ± 10% in algae and 56 ± 5% in daphnids	(Lillicrap et al. 2011)
Fish	Double solvent extraction by sonicating the samples at 60 °C for 30 min (First extraction with MeOH (0.1% formic acid); second extraction with MeOH/acetone); extracts diluted for further cleanup by SPE cartridges	Extraction solvents: MeOH (0.1% formic acid) and MeOH/acetone (1:9); Eluents : MeOH/acetone (1:9)	114 ± 8%	(Lillicrap et al. 2011).
Air	Samples were collected using high volume samplers containing cleaned polyurethane foams, XAD-2 resin, and quartz fiber filters; spiked with IS and soxhlet extraction with for 24 h	MeOH	69–101%	(Gan et al. 2014)

(< 1 week) (Lange et al. 2012). Mawhinney et al. (2011) and Oppenheimer et al. (2011) described the protocol in details from sampling to analysis for SUC in drinking water which employing the sodium azide (or omadine) and ascorbic acid to quench any residual oxidants. But the applicability of this stabilization procedure was only made plausible by comparison with those for PPCPs. Further studies concerning the stability and storing conditions for specific ASs in different environmental matrices were quite important and necessary, particularly the non-persistent ASs (such as ASP, CYC, and SAC) and complicated mediums. Certain recommendations and guidelines of ASs stability should be incorporated into quality assurance protocols in the future.

### Distribution patterns of ASs in natural environments

The large consumption of ASs inevitably results in their entry into the environment as most of the ASs are excreted without transformation and metabolism after ingestion (Chattopadhyay et al. 2014; Findikli and Turkoglu 2014; Sang et al. 2014). Numerous ASs, especially ACE, CYC, SAC, and SUC, are widely detected in various environmental medium due to their high solubility and mobility, such as wastewater, sludge, surface water, groundwater, and drinking water (Mawhinney et al. 2011; Oppenheimer et al. 2011; Scheurer et al. 2009; Subedi and Kannan 2014; Tran et al. 2014). The common environmental sources and potential fates of ASs are depicted in Fig. 2 (Feng et al. 2013).

### Municipal wastewater

Wastewater treatment plants (WWTPs) are commonly regarded as the most important barriers to prevent the entry of pollutants into environments. The ineffective removal of these emerging organic pollutants by WWTPs would result in their huge release into environments and the potential environmental pollution. Thus, it caused great concern when ASs were firstly reported to be

detected in WWTPs effluents (Brorströmlundén et al. 2013). From then on, various studies on the determination of ASs concentration as well as their fates in WWTPs have been investigated. The ASs concentration varies significantly from ng/L to µg/L in wastewater, depending on the different regions and types of ASs (as shown in Table 4).

In Europe, Sweden firstly reported the detection of SUC in WWTPs with the concentration of 3.5–7.9 µg/L in influents and 1.8–10.8 µg/L in effluents in 2007 (Brorströmlundén et al. 2008). The higher concentration of SUC in effluents than that of influents may be attributed to the release of sorped SUC on the suspended particulates of influents after the treatment of WWTPs (Subedi and Kannan 2014). Various ASs with different concentrations were also detected in the wastewater of Germany, Switzerland, Spain, etc. (as shown in Table 4). The concentrations of ASs in effluents were obviously decreased due to the removal in WWTPs. But the removal efficiency varied greatly among different ASs, which could be up to 41% for ACE, about 20% for SUC, and more than 90% for SAC and CYC (Scheurer et al. 2009). The CYC showed high concentrations in the influents of WWTPs, but the high removal efficiency contributed to the low detection in effluents. Conversely, the ACE and SUC still exhibited high concentrations in effluents.

In North America, Bikram et al. detected four ASs (SUC, ACE, SAC, and ASP) with high detection frequency in WWTPs near New York states in the USA (Table 4) (Subedi and Kannan 2014). Ferrer et al. and Oppenheimer et al. considered the SUC as the most widely detected AS around USA with the average concentration of 1.5 µg/L while the detection frequency of SAC and ASP was low (Ferrer and Thurman 2010; Oppenheimer et al. 2011). The highest concentration was even observed to be 119 µg/L in WWTPs by Mead et al. (2009). Additionally, various ASs were detected in Canadian wastewater and SUC was also the prevailing AS (Van Stempvoort et al. 2011b).

In Asia, Tran et al. found that the concentrations of ASs in raw domestic wastewater samples in Singapore varied between 4.33 and 135.76 µg/L for ACE, 6.77 and 54.28 µg/L for CYC, 10.14 and 135.76 µg/L for SAC, and 0.29 and 4.71

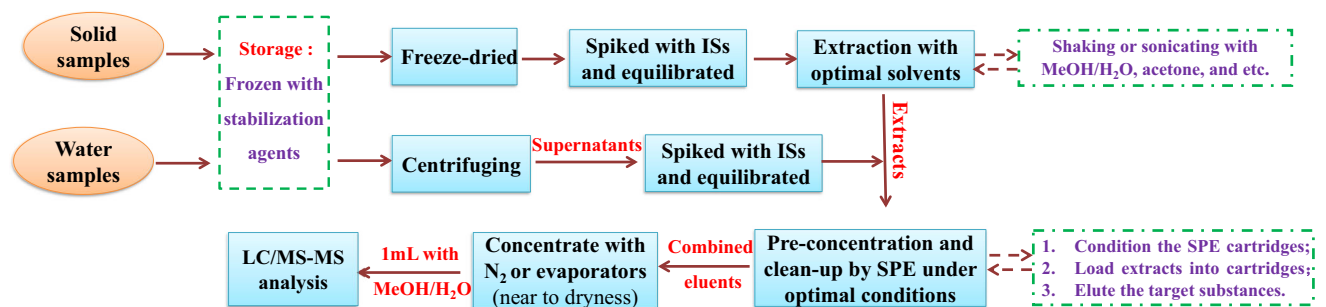
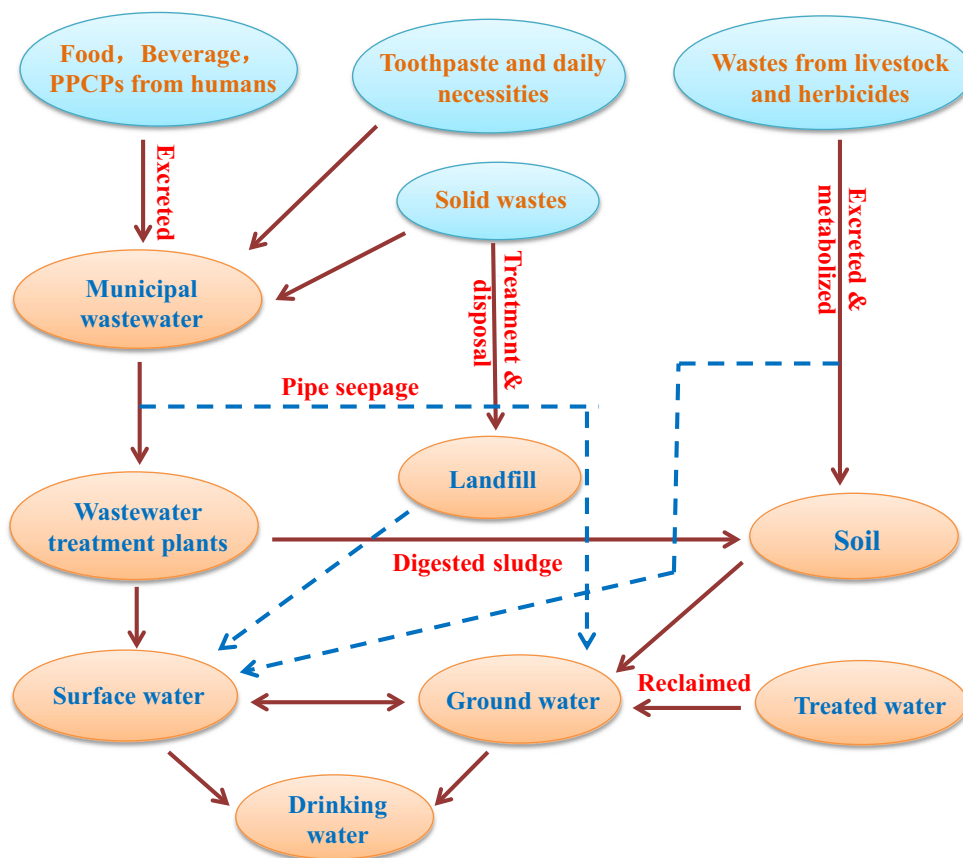


Fig. 1 Proposed ASs extraction procedures from environmental samples



**Fig. 2** Sources and fates of typical ASs in natural environments



$\mu\text{g/L}$  for SUC (Tran et al. 2014). In India, SAC was at the highest mean concentration of 303  $\mu\text{g/L}$ , followed by CYC and SUC in influents (Subedi et al. 2015). The average concentration of SAC in the influent of India WWTPs was 15 times higher than that in Spain (Ordóñez et al. 2012) and 20 times higher than that in the USA (Subedi and Kannan 2014). But the average concentration of CYC in influents from Indian WWTPs was 43 times lower than that in Germany (Scheurer et al. 2009). The SUC level was similar to Europe (Buerge et al. 2009; Loos et al. 2013; Qi et al. 2015; Scheurer et al. 2009) but was substantially lower than that in the USA (Subedi and Kannan 2014). Contrarily, ACE was significantly lower than that in Europe (Buerge et al. 2009; Scheurer et al. 2009) but at similar levels with the USA, Korea, and Saudi Arabia (Alidina et al. 2014; Berset and Ochsenbein 2012; Subedi and Kannan 2014).

In China, the concentrations of the investigated ASs in Tianjin WWTPs were generally in the order of  $\text{CYC} > \text{ACE} > \text{SAC} > \text{SUC} > \text{NHDC} > \text{ASP} > \text{NEO}$ , with concentrations ranging from 10  $\text{ng/L}$  to 20  $\mu\text{g/L}$ . In the effluents, NHDC, NEO, and ASP were not detected and the average concentrations of CYC and SAC dramatically decreased to 0.16 and 0.28  $\mu\text{g/L}$ , respectively. The results indicated the high efficiency of WWTPs in removing these ASs. However, SUC and ACE were persistent ASs

in the investigated WWTPs, and their discharged levels into receiving waters were higher than 1.0 and 15  $\mu\text{g/L}$ , respectively (Gan et al. 2013a). The main AS in WWTPs effluents of Beijing was also the SUC with the concentration of 2.7–3.5  $\mu\text{g/L}$  (Qi et al. 2015).

## Sludge

Due to the high water solubility and octanol–water partition coefficients of ASs, no significant adsorption of ASs to sludge particles are expected and thus the related studies are quite few. To our best knowledge, only five literatures reported the ASs distribution in sludge. In fact, due to the high loadings into WWTPs resulting in their transfer from aqueous phase to sludge (Scheurer et al. 2009), high levels of ASs were also detected in sludge (shown in Fig. 3).

In Sweden, the presence of SUC in sludge was evaluated in two studies during 2007. The levels of SUC ranged from 7 to 429  $\mu\text{g/kg}$  (dry weight, dw) with high detection frequency (63–83%) (Brorströmlundén et al. 2008). In Spain, the ASP and NHDC were not detected but the ACE, CYC, and SUC were found in all the analyzed sludge samples with different distribution patterns. SUC and ACE were both found in the primary sludge and

**Table 4** Typical ASs concentration (µg/L) in influents and effluents in WWTPs worldwide

Main markets	Countries	Sampling time	SUC		ACE		CYC		SAC		ASP		References
			Influ.	Efflu.	Influ.	Efflu.	Influ.	Efflu.	Influ.	Efflu.	Influ.	Efflu.	
Europe	Switzerland	2008	2.0–9.1	2.0–8.8	12–43	14–46	1–65	< 0.45	3.9–18	< 1.8	–	–	(Buerge et al. 2009)
	Sweden	2007	3.5–7.9	1.8–10.8	–	–	–	–	–	–	–	–	(Brorströmlundén et al. 2008)
North America	Germany	2010	1.7–4.1	0.7–4.9	–	2.3	–	–	–	–	–	–	(Neset et al. 2010)
		2009	1.9–2.9	2.5	1.7–3.2	2.3	≤ 190	≤ 2.8	34–50	< 2.8	–	–	(Lange et al. 2012)
	2010	< 1	0.8–0.9	34–50	≤ 20	–	–	–	–	–	–	(Ordonez et al. 2013)	
	2011	0.4–1.5	0.4–1.5	8.2–37	11–39	31.2	18.3	20.7	7.5	–	–	–	(Morlock et al. 2011)
Asian	USA	2011	4.2	16.5	25.5	32	–	–	5	–	–	–	(Oppenheimer et al. 2011)
	Canada	2014	27.7	29.6	1.08	–	–	–	16.4	0.42	0.49	0.11	(Subedi and Kannan 2014)
Asian	Singapore	2011	17	–	3.5	–	0.133	–	0.147	–	–	–	(Van Stempvoort et al. 2011a)
	India	2014	0.29–4.7	–	4.3–135.7	–	6.8–54.3	–	10.1–135.8	–	–	–	(Tran et al. 2014)
	India	2015	0.38–3.4	0.92–2.5	< 0.085	< 0.39	0–8.18	0.01–2.2	143–369	≤ 21.1	–	–	(Subedi et al. 2015)
	Israel	2016	1.1–1.9	0.79–1.87	0.56–0.86	0.45–0.89	–	–	–	–	–	–	(Anumol et al. 2016)
	China	2009	–	> 10	0.86–17	> 50	–	–	–	–	–	–	(Lange et al. 2012)
	China	2013	0.15–1.9	1.5	–	1.7–17	3.2–21	0.17	1.4–9.1	0.28	0.04	–	(Gan et al. 2013b)
		2015	3.21–5.04	2.7–3.5	–	–	–	–	–	–	–	–	(Qi et al. 2015)

secondary sludge, but exhibited higher concentrations in secondary sludge. Conversely, the concentration of CYC was higher in primary sludge than that in secondary sludge. The SAC was detected in all primary sludge samples, but only in one sample of the secondary sludge (Ordonez et al. 2013).

The detection frequency of SUC, SAC, ACE, and ASP in the USA sludge samples was respectively 55, 73, 100, and 93%. Their mean concentration ranged from 118 (ACE) to 506 µg/kg dw (SUC) (Subedi and Kannan 2014), which were similar to those reported in Spain and Sweden (Lange et al. 2012; Ordonez et al. 2013).

In India, SAC, CYC, SUC, and ACE were detected in sludge samples with the detection frequency from 75 to 100% (Subedi et al. 2015). The average concentration of ACE was 15.8 µg/kg dw, which was much lower than that in Spain and the USA (Ordonez et al. 2013; Subedi and Kannan 2014). However, the average concentration of SAC (18,700 µg/kg dw) was 113 times higher than that reported in Spain (Ordonez et al. 2013). Also, the SUC was 5.8–62 times higher than that reported in Spain and Sweden (Brorströmlundén et al. 2008; Ordonez et al. 2013).

In Korea, a nationwide survey of ASs in sewage sludge from 40 representative WWTPs receiving domestic (WWTP<sub>D</sub>), industrial (WWTP<sub>I</sub>), or mixed (domestic plus industrial; WWTP<sub>M</sub>) wastewaters has been well investigated by Subedi et al. The obtained results indicated that the typical ASs of CYC, ASP, SAC, ACE, and SUC were detected in all sludge samples (Subedi et al. 2014). CYC was found at the concentration of > 49 µg/kg dw, but it was not detected consistently in sludge from WWTP<sub>D</sub> and WWTP<sub>M</sub> (detection frequency < 28%). ASP was found in 94% and 56% of the sludge samples in WWTP<sub>D</sub> and WWTP<sub>M</sub>, respectively, and the median concentration was about 300 µg/kg dw. The median concentration of SAC (50 µg/kg dw) was 2–5 times lower than that reported in Spain (Ordonez et al. 2013). ACE was found in 97% of sludge samples. The median concentration was 47 µg/kg dw (ranges 16–201 µg/kg dw) in sludge from WWTP<sub>D</sub>, which was similar to that reported in sludge from Spain (Ordonez et al. 2013). The median concentration of SUC (33.5 µg/kg dw) was approximately 2 times higher than that reported from Sweden (Brorströmlundén et al. 2008), similar to the primary sludge from Spain (Ordonez et al. 2013).

ASs were also detected in digested sludge of municipal WWTPs in Switzerland. The concentrations were respectively 23–43 µg/L for ACE, 1–6 µg/L for CYC, 10–16 µg/L for SAC, and 5–9 µg/L for SUC, which were similar to those previously found in untreated domestic wastewater, except for CYC (Buerge et al. 2011). It seemed that the main removal mechanism of WWTPs for ASs was transferring them from aqueous phase to sludge.

## Surface water

The inefficiency of WWTPs in removing ASs, especially SUC and ACE, has been extensively reported (Ma et al. 2017; Scheurer et al. 2009; Soh et al. 2011; Torres et al. 2011). The discharged effluent from WWTPs is an important source of ASs in natural aquatic environments (Buerge et al. 2009; Gan et al. 2013a; Loos et al. 2013). The SUC and ACE are the most commonly detected ASs in surface water (Table 5).

An extensive study on the distribution of SUC in the stream and river of 27 European countries was performed (Loos et al. 2009). Data obtained from Switzerland, Sweden, etc. indicated that the SUC concentrations (detection frequency 50%) in these countries were as high as 1 µg/L (Loos et al. 2009). However, some recent investigations showed that the highest concentration of SUC in surface water of Sweden and Switzerland was respectively reduced to 0.47 and 0.60 µg/L (Scheurer et al. 2011; Sharma et al. 2012). The reason might attribute to the government ban of SUC in some beverages (Neset et al. 2010). The SUC concentration was much lower in Germany and Eastern Europe (Loos et al. 2009). SUC was also detected in the surface water of the USA and Singapore with high concentrations (Ferrer and Thurman 2010; Torres et al. 2011; Tran et al. 2014).

As to the ACE, Buerge et al. (2009) detected its presence in 4 rivers and 9 lakes in Switzerland with an average concentration of 2.8 µg/L. A distinct linear correlation of ACE concentrations and population density was found. The ACE was mainly derived from municipal wastewater as it was only detected in the surface water with sewage effluents discharge (Müller et al. 2011). Similar results have also been concluded by Buerge et al. and Loose et al. High consumption and stability during wastewater treatment resulted in the extreme high emissions of ACE from WWTPs (Buerge et al. 2009; Loos et al. 2013). However, ACE was much lower in Canada and Singapore in all detected stream water (Tran et al. 2014; Van Van Stempvoort et al. 2011b).

In China, various ASs have been detected in surface water (Table 5). The concentrations of persistent ASs: SUC and ACE, were comparable to or a little lower than those in the USA and European countries (Kokotou et al. 2012). However, the concentrations of easily degradable ASs SAC and CYC were higher than those in Germany and Switzerland (Buerge et al. 2009; Scheurer et al. 2009). ASP, NEO and NHDC were also detected with relatively low concentrations, which were respectively 40, 9.3, and 220 ng/L (Gan et al. 2013a). Their wide detection may also attribute to the direct discharge of untreated wastewater near these sites though they were highly degradable (Kokotou et al. 2012). Perkola and Sainio (2014) found that the levels of ACE and SUC in rivers were correlated linearly with population equivalents of the WWTPs located within the catchment areas in Finland. Thus, the ACE and SUC were commonly considered as effective chemical

markers for tracing wastewater contamination in the aquatic environment (Fang et al. 2017).

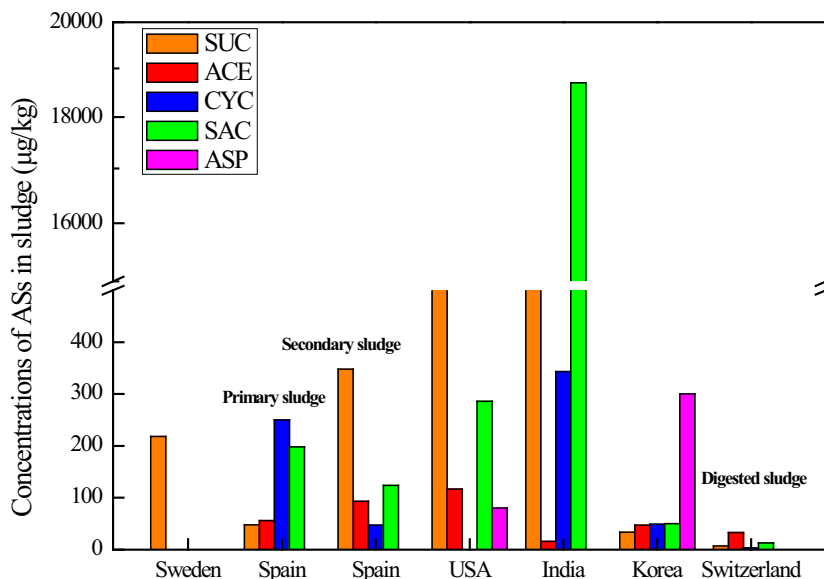
Moreover, the ASs were also found in the seawater. Mead et al. firstly reported the presence of SUC in North American coastal and open ocean waters with the concentration of up to 67–392 ng/L. The findings indicated the potentially widespread distribution of SUC from the USA waters due to the major oceanographic current of the Gulf Stream (Mead et al. 2009). Gan et al. also found the wide presence of ASs in Bohai regions of China. The concentration of SUC was up to 0.60 µg/L which was comparable to that in the USA (Mead et al. 2009). The highest concentrations of ACE, SAC, and CYC could be up to 9.9, 1.3, and 1.5 µg/L, respectively (Gan et al. 2013b). Meanwhile, they found that the sites with higher ASs concentrations were all located near estuaries or municipal discharge outlets which could receive the inland inputs. The ACE, SAC CYC, and SUC detected in the seawater near Hongkong were at the concentration of 0.34, 0.25, 0.23, and 0.2 µg/L (Xu and Gan 2016).

## Groundwater

The entry of ASs into groundwater could be achieved through wastewater ponds, leakage of septic tanks or sewer pipes, landfills, localized spills of food and beverages, agricultural sources or industrial sources, etc. (Buerge et al. 2009; Buerge et al. 2011).

ACE and SUC were the most commonly detected ASs in groundwater (Table 5). In Austria and Bavaria, the ACE in groundwater was up to 4.6 µg/L with high detection frequency (Buerge et al. 2009; Storck et al. 2016). Extensive distribution of ACE was also observed in Switzerland aquatic environments. ACE was detected in 65 out of the 100 analyzed groundwater samples and could be up to 4.7 µg/L in some samples. High ACE concentrations (~ 2.6 µg/L) were even observed in tap water originating from groundwater sources. The contamination might be caused by the infiltration of wastewater-polluted surface water into groundwater samples (Buerge et al. 2009). Scheurer et al. analyzed the groundwater samples near the soil aquifer treatment in Germany and found that the ACE concentrations in monitoring wells were similar to those of the wastewater effluents. In addition, SUC was the second main found AS with a concentration of 1.2 to 11 µg/L (Scheurer et al. 2009). The ACE and SUC were also detected in the Canadian groundwater with high detection frequency (Van Stempvoort et al. 2011b). But the concentration of SUC in groundwater samples was much lower around America (Ferrer and Thurman 2010). The high detection frequency and concentrations of ACE and SUC in the different groundwater samples may attribute to their persistent characteristics which were difficult to biodegrade (Buerge et al. 2009; Scheurer et al. 2009).

**Fig. 3** Concentrations of typical ASs in the sludge of different WWTPs



The other ASs, such as SAC and CYC, were less detected in groundwater. No SAC and CYC detection have been reported in any groundwater samples in Europe before 2009 (Buerge et al. 2009). Van Stempvoort et al. firstly detected the SAC and CYC in multiple groundwater samples of Canada (> 1 µg/L), especially those samples near municipal wastewater ponds (Scheurer et al. 2009; Van Stempvoort et al., 2011b). Buerge et al. also reported that the concentrations of SAC in groundwater samples could be up to 0.26 µg/L due to manure application in agricultural soils (Buerge et al. 2011). The detection of highly degradable SAC and CYC with high concentrations in groundwater at some sites may indicate that the biodegradation and/or sorption processes were limited or inhibited under certain conditions.

### Drinking water

The studies on ASs determination in drinking water are quite few. The first measurement was conducted in Switzerland in 2009 (Buerge et al. 2009). The ACE was found in drinking water with the concentrations of up to 2.6 µg/L by utilizing the groundwater as source water. However, the concentration of ACE in the end-pipe was reduced to 0.02–0.07 µg/L after oxidation treatment. Also, Scheurer et al. found that the ACE was up to 0.76 µg/L in water samples from 6 drinking water treatment plants (DWTPs) in Germany (Scheurer et al. 2010). The SUC was also observed in the drinking water systems of America with high detection frequency. For example, Mawhinney et al. found that the SUC was present in the source water of 15 out of 19 DWTPs, finished water of 13 out of 17 DWTPs, and distribution system water of 8 out of 12 DWTPs tested (Mawhinney et al. 2011). The results further indicated the persistence of ACE and SUC in environments.

However, in China, not only the persistent SUC and ACE but also those non-persistent NEO, CYC, and SAC were all detected in the influents of DWTPs and the drinking water (Gan et al. 2012). The large consumption of these ASs in China, as well as the ineffective removal in water treatment works, may account for this (Mckie et al. 2016). The concentrations of ASs in drinking water (ug/L) are far below the acceptable level for humans and animals (Brusick et al. 2010; Viberg and Fredriksson 2011). However, the ozonation and photocatalytic reaction commonly occurred in water treatment processes. The transformation of ASs into more toxic intermediates during these processing units may be occurred which may exhibit harmful effects to some sensitive living organisms. Therefore, more researches focusing on the transport fate of ASs in drinking water are required (Ghosh et al. 2018; Hu et al. 2017; Ren et al. 2016; Sang et al. 2014).

### Soils

The soils are also easily contaminated by the ASs. ASs could enter the soils through various routes, such as the irrigation of treated wastewater, leaky sewers, or the application of sludge as fertilizer in agriculture (seen in Fig. 2) (Buerge et al. 2011; Subedi et al. 2015). Animals manure and metabolites of certain sulfonylurea herbicides (such as the SAC) are also the main polluted sources (Buerge et al. 2011; Ma et al. 2017). For example, the permission of SAC as an additive in piglet feed resulted in the high concentrations of SAC in liquid manure (up to 12 mg/L after 2 months storage) (Buerge et al. 2011). Ma et al. found that the mass loadings of the ASs into soils from the investigated pig farms (annual output of 13,500 pigs) were estimated up to 112 kg/year for SAC, 35.1 kg/year for CYC, and 6.3 kg/year for ACE (Ma et al. 2017). The

**Table 5** ASs distributions in different aquatic environments

Aquatic environment	Countries	Detected ASs	Concentrations ( $\mu\text{g/L}$ )	References
Surface water (rivers and lakes)	UK, Belgium, France, Switzerland, Italy, Spain, Netherlands, Norway, and Sweden	SUC	< 1	(Loos et al. 2009)
	Germany and Eastern Europe	SUC	< 0.1	(Loos et al. 2009)
	Germany	SAC and CYC	SAC: 0.05; CYC: 0.15	(Scheurer et al. 2009)
	Switzerland	ACE, SAC, and CYC	ACE: 2.8 (average); SAC: 0.18; CYC: 0.13	(Buerge et al. 2009)
	Switzerland	ACE	10	(Müller et al. 2011)
	USA	SUC	1.8	(Ferrer and Thurman 2010).
	Canada	ACE	< 0.1	(Van Stempvoort et al. 2011)
	Singapore	SUC and ACE	< 0.53 for SUC; 0.78 for ACE	(Tran et al. 2014)
	China	ACE, CYC, SUC, SAC, NEO, NHDC, and ASP	SUC: 0.18–0.35; ACE: 1.6–7.6; SAC: 0.21–1.1; CYC: 0.12–0.67; ASP: 0.04; NEO: 0.009, and NHDC: 0.22	(Gan et al. 2013)
	North American	SUC	0.067–0.392	(Mead et al. 2009)
Sea water	China (Bohai regions)	SUC, ACE, SAC, and CYC	SUC: 0.60; ACE: 9.9; SAC: 1.3; CYC: 1.5	(Gan et al. 2013)
	China (Hongkong)	ACE, SAC CYC, and SUC	ACE: 0.34; SAC: 0.25; CYC: 0.23; SUC: 0.2	(Xu and Gan 2016)
	Austria, bavaria	ACE	Up to 4.6	(Storck et al. 2016).
	Switzerland	ACE	0.03 (average); 4.7 (highest)	(Buerge et al. 2009)
	Switzerland	SAC	0.26	(Buerge et al. 2011)
	Germany	ACE and SUC	ACE: 30–58; SUC: 1.2–11	(Scheurer et al. 2009)
	Canada	ACE, SUC, SAC, and CYC	ACE: 0.06–33.6; SUC: 11–24; SAC and CYC (> 1)	(Van Stempvoort et al. 2011)
	USA	SUC	0.6–2.4	(Ferrer and Thurman 2010)
	Switzerland	ACE	~ 2.6 (source water from groundwater); 0.02–0.07 (in the end-pipe with oxidation treatment)	(Buerge et al. 2009)
	Germany	ACE	0.76	(Scheurer et al. 2010)
Drinking water	America	SUC	0.05–2.9 (source water); 0.05–2.4 (finished water and distribution system water)	(Mawhinney et al. 2011)
	China	NEO, CYC, SAC, SUC, and ACE	< LOD–0.58 0.02–0.5 (finished water)	(Gan et al. 2012)



contamination of ASs in soil may pose a risk to groundwater and plants bioaccumulation (Ma et al. 2017).

However, the investigations of the ASs occurrence in soils are also limited. Ma et al. demonstrated that the SAC, CYC, and ACE were widely detected in soil samples with the ranges of 0.92–21.8  $\mu\text{g}/\text{kg dw}$  for ACE, 3.87–17.5  $\mu\text{g}/\text{kg dw}$  for SAC, and 2.20–6.78  $\mu\text{g}/\text{kg dw}$  for CYC while SUC were below the LOD (Ma et al. 2017). Buerge et al. (2011) also found the existence of ASs in soils when using the pig manure and digested sludge as fertilizers. Gan et al. have investigated the variations of ASs in China. The SAC, CYC, and ACE were found in all of the investigated soil samples with the concentrations ranging from 0.22 to 34.7  $\mu\text{g}/\text{kg dw}$ , 2.87 to 183  $\mu\text{g}/\text{kg dw}$ , and 4.61 to 336  $\mu\text{g}/\text{kg dw}$  in Northern China, respectively, while ranging from 0.11 to 28.1  $\mu\text{g}/\text{kg dw}$ , 0.01 to 1280  $\mu\text{g}/\text{kg dw}$ , and 0.08 to 569  $\mu\text{g}/\text{kg dw}$  in Southern China, respectively. No significant difference was found between Northern and Southern China (Gan et al. 2014).

The highly contaminated soils by ASs would result in the uptake by plants. ASs were found in the vegetables planted near ASs contaminated farms with the concentrations of ranging from 51.0 to 108  $\mu\text{g}/\text{kg dw}$  for ACE, 81.6 to 181  $\mu\text{g}/\text{kg dw}$  for SAC and 56.7 to 275  $\mu\text{g}/\text{kg dw}$  for CYC (Ma et al. 2017). However, in contrast to the municipal WWTPs, the ASs could dissipate rapidly in soils via the metabolism of functional microorganisms, plant absorption, photodegradation, etc. The half-lives of CYC, SAC, ACE, and SUC were respectively reported to be 4.3–5.9, 2.7–4.2, 8.4–12.3, and 7.3–10.8 days in soils by Ma et al. The ASs were eventually decreased to 13% for ACE, 1% for SAC and CYC, and no detection for SUC (Ma et al. 2017). Similar results were also found by Buerge et al. in soil incubation experiments (Buerge et al. 2011).

## Atmosphere

The monitor of ASs in the atmosphere is commonly ignored. Gan et al. firstly confirmed the presence of ASs in the atmosphere. They found that CYC and ACE were the predominant ASs in the atmosphere. SUC was only found in particulate phase with the concentration of up to 13  $\text{pg}/\text{m}^3$ . They further analyzed 98 outdoor dust samples in China. The SAC, CYC, and ACE were detected in all samples with concentrations ranging from 2.89 to 1860  $\mu\text{g}/\text{kg}$ , 0.52 to 6450  $\mu\text{g}/\text{kg}$ , and 0.56 to 861  $\mu\text{g}/\text{kg}$  in Northern China, respectively; while those levels varied from 1.03 to 338  $\mu\text{g}/\text{kg}$ , 0.70 to 1370  $\mu\text{g}/\text{kg}$ , and 0.49 to 217  $\mu\text{g}/\text{kg}$  in Southern China, respectively. No significant difference was found between Northern and Southern China. But they showed positive correlations with population density since higher levels of ASs were detected in the densely populated areas (Gan et al. 2014).

They also concluded that the NEO, NHDC, and ASP were mainly present in the gas phase, while the SUC, SAC, CYC, and ACE were in the particle-associated phase. The ASs may enter the atmosphere in a particle-associated form with airborne dust and the distribution between the different phases (i.e., air and particle) is a key process affecting the occurrences and fates of ASs in the atmosphere (Gan et al. 2013a).

Overall, the high detection frequency combined with high levels of ASs in the dust samples of China indicated that the ubiquitous presence of ASs. Currently, there is no information reporting the potential risks of ASs in the atmosphere to surface environments and living organisms (through dust fall and inhale with  $\text{PM}_{2.5}$ ), but further researches are required to confirm it. The ASs may undergo certain reactions in the atmosphere (such as photodegradation) and form unknown toxic metabolites.

## Main reasons for the highly varied ASs levels in different countries

As mentioned above, the concentrations of different ASs in environments are quite variable around the world. The distribution pattern of ASs in the USA was  $\text{SUC} > \text{SAC} > \text{ACE}$  (Subedi and Kannan 2014), whereas the European nations showed the prevalence of CYC, ACE, and SAC. For example, the pattern of ASs found in wastewater of Germany was  $\text{CYC} > \text{SAC}$ ,  $\text{ACE} > \text{SUC}$  (Scheurer et al. 2009). In Korean WWTPs, the distribution pattern of ASs was  $\text{ASP} > \text{SUC} > \text{ACE} > \text{SAC} > \text{CYC}$  (Subedi et al. 2014). The ASs distribution pattern ( $\text{SAC} > \text{CYC} > \text{SUC} \approx \text{ACE}$ ) in India was quite different from that reported in other countries (Anumol et al. 2016; Tripathi et al. 2006). Meanwhile, the rank order of average AS concentrations in sludge from the USA was as follows:  $\text{SUC} > \text{ASP} \approx \text{SAC} > \text{ACE}$  while it followed as  $\text{ASP} > \text{SAC} > \text{ACE} > \text{SUC}$  in South Korea. In general, the predominant AS in the USA was the SUC, whereas it was CYC in Europe and ASP in South Korea. SAC is the most widely detected AS in India.

Some researchers regarded the difference of market entry time as one of the possible reasons for the various ASs levels in different countries. For example, SUC was widely approved as a food and beverage additive in 1999, Switzerland in 2003, Sweden in 2004, and Germany in 2005 (Lange et al. 2012). It may partly explain the higher wastewater concentrations of SUC in the USA, Switzerland, and Sweden than that in Germany.

However, the analysis from the perspectives of consumption patterns and removal efficiency in WWTPs of different regions, especially the local consumption patterns, may better explain those evident differences.

## ASs consumption patterns

SUC was the most frequently used ASs in the USA, which was found in approximate 1500 products as compared to ACE (1103 products) and ASP (974 products) (Yang 2010). However, ASP was the most widely used ASs in food industries at extremely high concentrations (as much as 5602 mg/kg) in Korea (Ha et al. 2013). As to the India, SAC was the cheapest ASs in India (Tripathi et al. 2006). The Prevention of Adulteration of Food Act in India permits 100 mg/kg of SAC addition in carbonated drinks. Moreover, the other products, such as pan masala and crushed ice, were reported to contain as high as 24,300 mg SAC/kg (Tripathi et al. 2006). In Switzerland and German, much more CYC were consumed in food or beverages in order to obtain the same intensity of sweet taste of SAC, ASP, and SUC as they had much lower sugar equivalents (seen in Table 1). The ASs consumption on the basis of per capita loads, which was independent of the factors of discharge and population density, could better reflect the difference of consumption patterns (as shown in Table 6) (Lange et al. 2012; Neset et al. 2010; Subedi et al. 2015; Subedi and Kannan 2014; Subedi et al. 2014). For example, the obtained data indicated that the average loading of SUC into WWTPs in the USA was approximately 2 times higher than the loadings of SAC (Subedi and Kannan 2014), and respectively 12 and 100 times higher than those reported in Switzerland and Germany (Buerge et al. 2011). However, the average loadings of ACE in the USA were respectively 13 and 15 times lower than those reported in Switzerland and Germany (Scheurer et al. 2009; Van Stempvoort et al. 2011b).

The high consumption of ASs would generally result in the large discharge into environments. WWTPs are the first transferring stations for ASs and most of the consumed ASs are directly discharged into the WWTPs. Therefore, SUC was widely detected in the USA WWTPs with relatively high concentration. ASP was the predominant AS in both wastewater and sludge in Korea and SAC ranked the first order in India. In Switzerland and German, CYC was highly detected and

followed by ACE while SUC was less detected. Obviously, the mass load of ASs in WWTPs is in correspondence with the consumption pattern in specific regions.

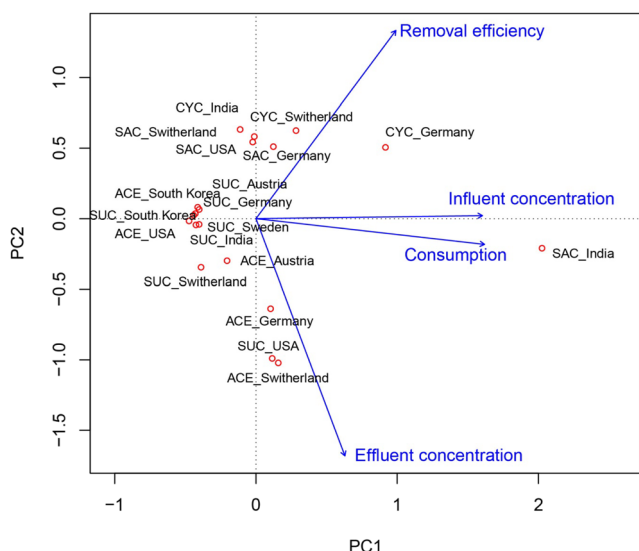
Additionally, the positive correlation of ASs consumption and their concentrations in the environment was further confirmed by the following results. Neset et al. found that the removal of ASs from daily products resulted in the strong decrease of ASs load. The SUC was reduced from 3.5–7.9 µg/L in the influents of Sweden WWTPs to 3 µg/L in 2010 due to the ban of Coco Cola, which was considered as the main source of SUC in municipal wastewater (Neset et al. 2010). The USA Food and Drug Administration banned CYC in 1970 from all foods due to its potential carcinogenic effects on experimental animals and thus nearly no CYC detection was found in the USA (Ferrer and Thurman 2010; Listed 1970; Mawhinney et al. 2011).

## ASs removal efficiency in WWTPs

WWTP is the most important barrier to prevent the entry of ASs into environments. Therefore, the removal efficiency of ASs in WWTPs affects their concentrations in environments. During secondary or tertiary wastewater treatment, the CYC, SAC, and ASP can be easily removed with the removal efficiency of 99, 90.3, and 68.3%, respectively (Subedi and Kannan 2014). For example, the CYC and SAC could be reduced from 190 and 40 µg/L in influents to 2.8 and 1 µg/L or lower in effluents of Germany WWTPs, respectively (Scheurer et al. 2009). However, the ACE and SUC are much less effectively removed by WWTPs, whose removal efficiency range from – 5 to 20% (Brorströmlundén et al. 2013; Buerge et al. 2009; Gan et al. 2013a; Li et al. 2018; Scheurer et al. 2009; Subedi and Kannan 2014), and from 2 to 41% (Buerge et al. 2009; Gan et al. 2013a; Neset et al. 2010; Scheurer et al. 2009; Subedi and Kannan 2014), respectively. Thus, the inefficient removal by WWTPs would result in the high levels of SUC and ACE in effluents. The ACE was

**Table 6** Estimated per capita load (mg/cap day) of ASs to WWTPs in different countries

Countries	SUC	ACE	CYC	SAC	References
Sweden	1.7–2.1 (in 2007) 0.76 ± 0.1 (in 2009)	–	–	–	(Lange et al. 2012) (Neset et al. 2010)
German	0.14–0.23	8–9.3	32.3–39	7.3–9.3	(Lange et al. 2012)
Switzerland	1.5 ± 0.6	10 ± 3.4	11 ± 6.7	3.9 ± 1.7	(Lange et al. 2012)
Austria	0.49	4.9	–	–	(Lange et al. 2012)
South Korea	0.12–0.33	0.09–0.16	0.02–0.08	0.07–0.15	(Subedi and Kannan 2014)
India	0.03–0.57	–	0.53–0.85	10.7–77.9	(Subedi et al. 2015)
USA	15.4–21.6	0.7–0.89	–	7.68–11.5	(Subedi et al. 2014)



**Fig. 4** Correlations of ASs distribution with the consumption and removal efficiency

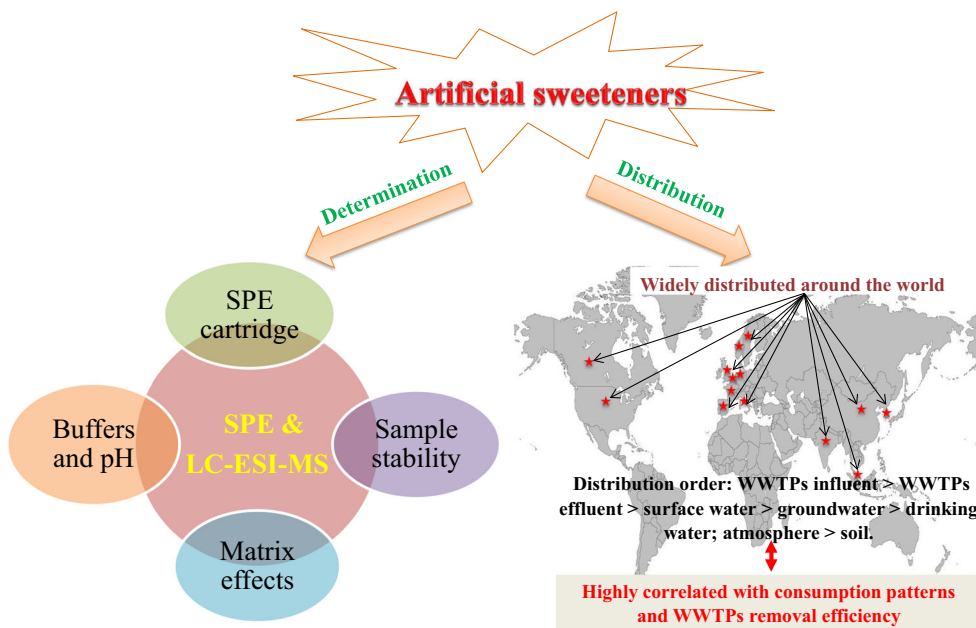
once found to be higher than 20 µg/L in the effluents (Castronovo et al. 2016; Scheurer et al. 2009).

The total mass load of ASs discharged through WWTPs effluents has also been reported. SUC is one of the most highly discharged (17.6 g/day/1000 people) ASs from the WWTPs in the USA, followed by SAC and ACE. These amounts correspond to an estimated annual discharge of 624 kg of SUC, 71.0 kg of SAC, 49.1 kg of ACE, and 2.90 kg of ASP from a WWTP that served a population of 100,000 (influent flow rate of 83,300 m<sup>3</sup>/day)(Subedi and Kannan 2014). Differently, SAC is the

most discharged AS from WWTPs in India, followed by SUC and CYC. These values correspond to an estimated annual discharge of 252 kg of SAC (due to high influent concentrations), 16.0 kg of SUC, and 5.84 kg of CYC from a WWTP that served an average population of 325,000 with an average inflow rate of 21,000 m<sup>3</sup>/day (Subedi et al. 2015). As shown in Table 6, the estimated load of SAC to WWTPs is 100 times higher than SUC. However, the proportion of SAC to SUC in the effluents was decreased remarkably. The reason could be also attributed to the different removal efficiency of SAC and SUC in WWTPs. The removal efficiency of SAC was much higher than that of SUC (Scheurer et al. 2009). The estimated annual discharge of ASs from a WWTP (treatment capacity of 260,000 m<sup>3</sup>/day) in China was found in a different order: 1600 kg of ACE followed by 26 kg of SAC (Gan et al. 2013a).

Overall, the relationships of ASs consumption, concentrations in influents and effluents, and removal efficiency by WWTPs are illustrated in Fig. 4 based on the available information. The results indicate that the ASs in WWTPs influents and effluents both demonstrate the direct correlations with their consumption. The correlation coefficient is respectively 0.98 and 0.40. However, the effluent concentration is negatively related with the removal efficiency of WWTPs (correlation coefficient: -0.20). The analysis confirms the above assumption that the consumption patterns and WWTPs removal efficiency were the two main reasons for the different distribution of ASs in environment. Meanwhile, the consumption patterns possess more weightage over the removal efficiency in affecting the ASs occurrence in environments.

**Fig. 5** Influencing factors for ASs determination and their wide distribution in environments



## Conclusion and prospects

Overall, ASs are widespread in various environmental samples and the recovery efficiency and accurate determination of ASs in environments are also dependent on various external factors (Fig. 5). The SPE with LC-ESI-MS is the mainstream method for the ASs determination in environmental samples. However, a benchmark approach for the simultaneous detection of all ASs in environments has not been reported yet, which may be tailored to specific AS in particular sample.

Moreover, considering the large consumption and wide occurrence of ASs around the world, their potential ecological impacts should be further investigated. In addition, as the ASs distribution in environments is also related with their removal efficiency in WWTPs, it should take effective measures to reinforce the roles of WWTPs on the removal of trace organic pollutants, which would be effective to cut down the entry of ASs into environments.

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