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A comprehensive review on the analytical method, occurrence, transformation and toxicity of a reactive pollutant: BADGE

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ABSTRACT

Bisphenol A diglycidyl ether (BADGE)-based epoxy resin is one of the most widely used epoxy resins with an annual production amount of several million tons. Compared with all other legacy or emerging organic compounds, BADGE is special due to its toxicity and high reactivity in the environment. More and more studies are available on its analytical methods, occurrence, transformation and toxicity. Here, we provided a comprehensive review of the current BADGE-related studies, with focus on its production, application, available analytical methods, occurrences in the environment and human specimen, abiotic and biotic transformation, as well as the *in vitro* and *in vivo* toxicities. The available data show that BADGE and its derivatives are ubiquitous environmental chemicals and often well detected in human specimens. For their analysis, a water-free sample pretreatment should be considered to avoid hydrolysis. Additionally, their complex reactions with endogenous metabolites are areas of great interest. To date, the monitoring and further understanding of their transport and fate in the environment are still quite lacking, comparing with its analogues bisphenol A (BPA) and bisphenol S (BPS). In terms of toxicity, the summary of its current studies and Environmental Protection Agency (EPA) ToxCast toxicity database suggests BADGE might be an endocrine disruptor, though more detailed evidence is still needed to confirm this hypothesis in *in vivo* animal models. Future study of BADGE should focus on its metabolic transformation, reaction with protein and validation of its role as an endocrine disruptor. We believe that the elucidation of BADGEs can greatly enhance our understandings of those reactive compounds in the environment and human.

1. Introduction

2,2-bis(4-(2,3-epoxypropyl) phenyl) propane, also known as bisphenol A diglycidyl ether or BADGE. BADGE-based epoxy resin is one of the most widely used epoxy resins in the world (Chamorro-García et al. 2012). It is a reactive pre-polymer of BPA that is produced through the O-alkylation of BPA with epichlorohydrin (Lord 2014) (Fig. 1**a**). As a high production volume (HPV) chemical in the U.S., the production volume is reported to range from 1,000,000 ~ 20,000,000 lb in 2015 (EPA, 2016). It is widely used as a coating material in food and beverage cans (Lord 2014) monomer in the production of epoxy-based polymers and an additive for the elimination of surplus hydrochloric acid in polyvinyl chloride (PVC) organosol production (Gallart-Ayala et al. 2011; Wang et al. 2012a). BADGE can be easily transformed to its hydrolysis products or chlorinated products. Many of the transformation products are highly toxic (Marqueño et al. 2019; Satoh et al. 2004). Therefore, it is necessary to study the conversion pathway and derivatives of BADGE. Similarly, BADGE-related compound bisphenol F diglycidyl ether (BFDGE) is produced in the reaction between bisphenol F and epichlorohydrin (Szczepańska et al. 2018). It can also form hydrolysis products and derivatives such as BFDGE-2H_2O and BFDGE-2HCl. The production volume of BFDGE is yet unknown.

The chemical structure of BADGE is quite unique with two epoxides (electrophilic oxirane rings), resulting in its high reactivity. This property has been confirmed in an earlier study on its reaction with food components such as protein and amino acids that leads to its 'disappearance' in food packaging materials (Petersen et al. 2008). The analysis of BADGEs has always been a challenge due to these reasons as

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well as the laboratory background contamination (Liu et al. 2019). It is worth noting that majority of the environmental pollutants are non-reactive chemicals and yet we have quite limited knowledge on those reactive chemicals. Many of the emerging organic pollutants (EOPs) are reactive nowadays. For examples, more and more reactive flame retardants showed high-efficient flame retardancy and were proposed as a novel replacement for non-bonded flame-retardants in the market (Wazarkar et al. 2015; Xu et al. 2019)

Therefore, BADGE could be a classical model to study these reactive chemicals. To date, a limited number of studies have documented the widespread occurrences of BADGEs in the environment (Liu et al. 2019; Tran et al. 2016; Wang et al. 2012a; Xue et al. 2016a; Xue et al. 2015a; Xue et al. 2016b) and human specimens (Asimakopoulos et al. 2014a; Liu et al. 2019; Wang et al. 2012a; Wang et al. 2015; Xue et al. 2015b). A study reported BADGE may be equally or more harmful than BPA in triggering specific toxic effects such as cytotoxicity, raising concerns on its safety (Rosso et al. 2018). Therefore, an overview on environmental and toxicological studies of BADGE are of great significance to public health and regulation guidance.

There are more and more studies regarding the toxicity of BADGE and its biotransformation. It was reported to be mutagenic, genotoxic and cytotoxic in some cell models (Ramilo et al. 2006; Suárez et al. 2000). BADGE is also known as an antagonist of peroxisome proliferator-activated receptor gamma (PPAR γ) (Wright et al. 2000). In terms of its biotransformation, some studies revealed that a large proportion of BADGE is bio-transformed to many unknown metabolites which are yet to be thoroughly investigated (Climie et al. 1981; Nolan et al. 1981). In one of these studies, less than10% of BADGE remained unchanged in plasma in rats after oral dosage of 2-^{14}C-propane-labelled BADGE (Nolan et al. 1981).

The goals of this review are to compile and analyze the current state of knowledge on the occurrence of BADGE and its derivatives in the environment, consumer products, human exposure and toxicity; and to identify knowledge gaps and future research needs. The review is structured into seven topics: (a) production and application; (b) physicochemical properties and detection in sources; (c) analytical method of BADGEs; (d) occurrences in environmental matrices and human specimen; (e) biotransformation; (f) toxicity; and (g) conclusion and future studies.

2. Methodology

In the present review, we applied the U.S. Environmental Protection Agency (EPA) Estimation Program Interface (EPI) Suite Version 4.1 to calculate the properties such as log K_{ow} (octanol − water partition coefficient), log K_{aw} (air − water partition coefficient), bioconcentration factor (BCF) and bioaccumulation factor (BAF). The data of aggregate production volume in U.S. were curated from U.S. EPA's Chemical Data Reporting (CDR) database in 2016 (EPA, 2016) (https://www.epa.gov/chemical-data-reporting). Five keywords, namely dust, air, urine, blood and toxicity, along with each bisphenol analogue were applied to search against PubMed.gov (https://pubmed.ncbi.nlm.nih.gov/) to obtain the reference counts in Fig. 5**b**. For each bar graph, if the geometric mean (or median, whichever applicable) value is calculated from multiple sources, the error bar represents the standard deviation from these studies. If it is from a single source, the error bar represents the standard deviation (if available) or maximum/minimum values from that single study. For relative contribution calculation in Fig. 2**b**, the value was calculated based on the ratio of geometric mean (or median/mean if available) concentrations of a certain chemical to total BADGEs. The value was calculated by averaging the ratios if obtained from multiple sources. We curated the *in vitro* toxicity of BADGEs from the U.S. Environmental Protection Agency's (EPA) Toxicity Forecaster (ToxCast) (U.S.EPA, 2015) (https://www.epa.gov/chemical-research/toxicity-forecasting). The active results from these bioassays were obtained with their potency half-maximal activity concentrations (AC_{50}).

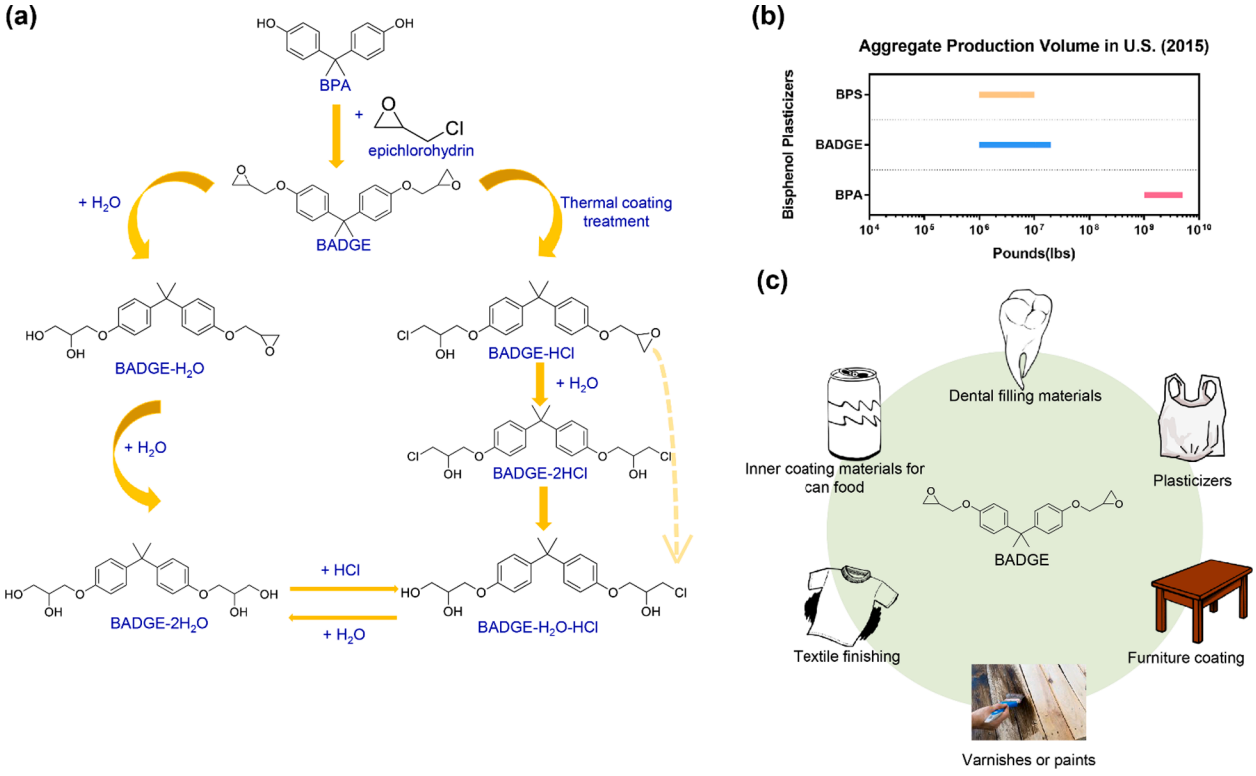


Fig. 1. (a) The synthesis of BADGE and reactions for the formation of BADGE-related compounds; modified from (Wang et al. 2012b); (b) The aggregate production volume of BADGE, BPS and BPA in U.S. (2015); data from U.S. EPA; CDR database, 2016. (https://www.epa.gov/chemical-data-reporting); (c) Widespread applications and sources of BADGE.

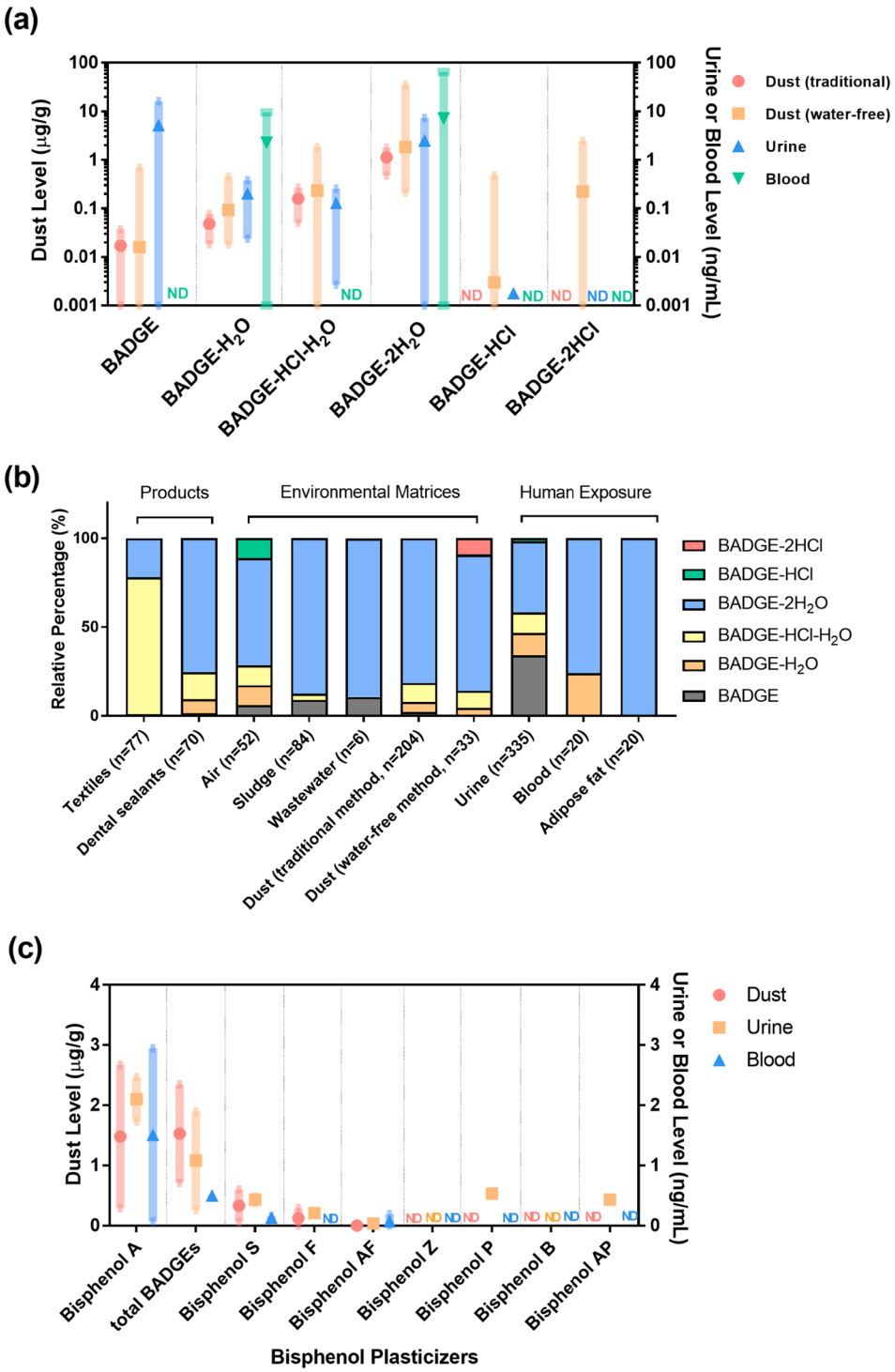


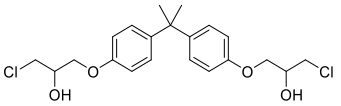
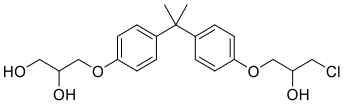
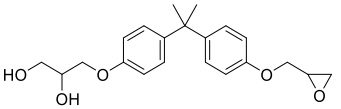
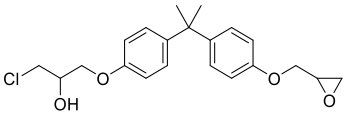
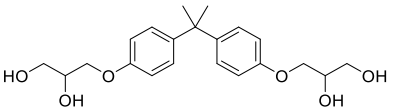
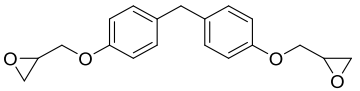
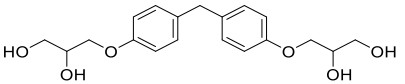
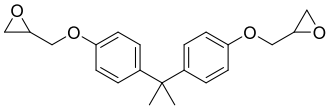
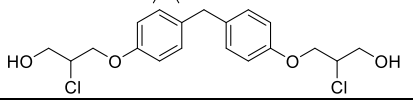
Fig. 2. (a) BADGE and its derivatives concentrations (μg/g in dust or ng/mL in urine or blood; Mean ± S.D.) quantified from house dust (traditional and water-free method), urine and blood samples (Asimakopoulos et al. 2014a; Liu et al. 2019; Tran et al. 2016; Wang et al. 2012a; Wang et al. 2012b; Xue et al. 2018; Xue et al. 2017; Xue et al. 2015a; Xue et al. 2016b); (b) The concentration ratio profiles of BADGEs from the products, environmental samples and human specimens; (c) The comparison of total BADGE concentrations with other bisphenol plasticizers in dust, urine and blood samples (μg/g; GM ± S.D.) (Chen et al. 2016; Dong et al. 2019; He et al. 2009; Jin et al. 2018; Li et al. 2020; Wan et al. 2013).

3. Production and applications

3.1. Production of BADGE

Bisphenol A diglycidyl ether (BADGE) is one of the most widely used epoxy resins in the world (Chamorro-García et al. 2012). It has been listed as a high production volume (HPV) chemical in the U.S as mentioned above. The production volume of BADGE in the U.S. was reported to be 1,000,000 ~ 20,000,000 lb between 2012 and 2015 from the U.S. EPA CDR database (EPA, 2016). As shown in Fig. 1**b**, its production volume in 2015 is comparable with BPS (1,000,000 ~ 10,000,000 lb) but much lower than BPA (5,000,000,000 ~ 1,000,000,000 lb). Additionally, BADGE has many unintended by-products (mainly its hydrolysis and chlorinated products) (Fig. 1**a and detailed in** Table 1**)**. For example, BADGE has two hydrolysis products BADGE-H_2O and BADGE-$2H_2O$. The chlorinated products (i.e., BADGE-HCl, BADGE-2HCl and BADGE-HCl-H_2O) are likely to be formed during the thermal coating treatment considering BADGE is also used as an additive to remove the hydrochloric acid (Gallart-Ayala et al. 2011). These derivatives are also unstable that can be further hydrolyzed.

Table 1
Calculated physicochemical properties of BADGEs based on EPI Suite™-Estimation program interface (EPIWEB 4.1).

Compound	Abbreviation	Structure	Molecular Formula	CAS #	M.W.	Log K_{OW}[a]	Log K_{OA}[b]	Solubility (mg/L) at 25 °C	BAF[c]	BCF[d]
Bisphenol A bis(3-chloro-2-hydroxypropyl) ether	BADGE-2HCl		$C_{21}H_{26}Cl_2O_4$	4809–35-2	411.34	4.57	14.77	0.31	900.4	887.5
Bisphenol A (3-chloro-2-hydroxypropyl) (2,3-dihydroxypropyl) ether	BADGE-HCl-H_2O		$C_{21}H_{27}ClO_5$	227947–06-0	394.89	3.25	14.44	5.54	95.11	95.1
Bisphenol A bis(2,3-dihydroxypropyl) ether	BADGE-H_2O		$C_{21}H_{26}O_5$	76002–91-0	358.43	1.93	14.10	96.18	77.36	77.36
Bisphenol A (3-chloro-2-hydroxypropyl) glycidyl ether	BADGE-HCl		$C_{21}H_{25}ClO_4$	13836–48-1	376.87	4.00	15.22	5.25	480.5	479.4
Bisphenol A bis(2,3-dihydroxypropyl) ether	BADGE-2H_2O		$C_{21}H_{28}O_6$	5581–32-8	376.44	1.93	14.10	96.18	6.581	6.581
bisphenol F diglycidyl-ether	BFDGE		$C_{19}H_{20}O_4$	2095–03-6	312.36	3.26	12.25	17.20	117.1	117.1
Bisphenol F bis(2,3-dihydroxypropyl) ether	BFDGE-2H_2O		$C_{19}H_{24}O_6$	72406–26-9	348.39	1.34	13.76	452.60	1.993	1.993
Bisphenol A diglycidyl ether	BADGE		$C_{21}H_{24}O_4$	1675–54-3	340.42	3.84	12.59	3.69	400.5	399.9
Bisphenol F bis(2-chloro-1-propanol) ether	BFDGE-2HCl		$C_{19}H_{22}Cl_2O_4$	374772–79-9	385.28	3.98	14.43	1.51	291.8	291.7

[a] K_{ow} = octanol–water partition coefficient
[b] K_{aw} = air–water partition coefficient
[c] BCF = bioconcentration factor (L/kg wet weight)
[d] BAF = bioaccumulation factor (L/kg wet weight)

3.2. Applications and detection in sources

The presence of BADGE-related compounds (BADGEs) is ubiquitous in our daily life. The major application fields of BADGEs are primarily in sealants, coating, paints, fillers for textiles, packaging materials, or even dental filling material **(**Fig. 1**c)** (Møller et al. 2012). One big concern of BADGE was raised by its application in canned food coating/food packaging materials that can migrate into foods when heated and further consumed by human (Coulier et al. 2010). Root canal sealers are commonly used to endodontically treat teeth with periapical infections and some materials are based on epoxy resin contain BADGE (Graunaite et al. 2018).

Concentrations of BADGEs were previously determined in 70 dental sealants collected from the U.S. market (Xue et al. 2018). Among all the tested compounds, BADGE-2H$_2$O was most abundant, found at concentrations of up to 1,780 μg/g. The geometric mean (GM) concentration of total BADGEs was 47.8 μg/g. Therefore, leaching of these compounds into saliva can be a human exposure pathway. In another source of textiles, concentrations of BADGEs and BFDGEs were determined in 77 textiles and infant clothing collected from Albany, New York, U.S. (Xue et al. 2017). BFDGE was detected as the predominant compound, with a mean concentration of 13.6 ng/g, followed by BADGE-HCl-H$_2$O (7.32 ng/g) and BADGE-2H$_2$O (1.92 ng/g).

4. Physicochemical properties of BADGEs

The physicochemical properties and structures of BADGEs are summarized in Table 1. In general, the structures of these compounds show high similarity in backbones containing two benzenes, but their side-chain functional groups are different. Both BADGE and BFDGE have epoxide, a cyclic ether with a three-atom ring, which makes them highly reactive. Additionally, these electrophilic oxirane rings are subject to reaction with nucleophilic species (Petersen et al. 2008). To date, data on experimentally determined physicochemical properties of BADGEs are generally limited. Through calculation, the estimated log K_{ow} values of BADGEs range from 1.34 to 4.57, which all below 5, suggesting that they are less likely to bioaccumulate according to Stockholm Convention (Lallas 2001). The estimated log K_{ow} of hydrolysis derivatives such as BADGE-H$_2$O, BADGE-2H$_2$O and BFDGE-2H$_2$O is comparably lower, indicating their hydrophilic properties. While BADGE/BFDGE and their chlorohydroxy derivatives are relatively more hydrophobic. The estimated log K_{OA} values of BADGEs range from 12.25 ~ 15.22, suggesting these chemicals are semi-volatile compounds (SVOCs). The BCF values of BADGE and its derivatives range from 1.99 to 887.5. The BCF values of BADGE and some derivatives BADGE-2HCl and BADGE-HCl are comparably higher (> 400 L/kg) while hydrolysis derivatives such as BADGE-2H$_2$O and BFDGE-2H$_2$O are generally low (<10 L/kg). These chemicals are generally not bioaccumulative since the criterion of above 2000 L/kg is considered to be bioaccumulative by the European Union Registration, Evaluation and Authorization of Chemicals (REACH) regulation (Arnot et al. 2006).

5. Analytical method of BADGEs

The analysis of BADGEs as a group of emerging organic contaminants can be quite challenging for a couple of reasons. The first concern is the hydrolysis potential of BADGEs. Two epoxy rings of BADGE are highly reactive and can be hydrolyzed with half-lives of approximately 2 days at pH 7 and 35 °C (Lane et al. 2015). For solid samples (e.g., dust), a water-free environment during the sample extraction and clean-up steps should be ensured, otherwise can lead to low recovery issues. The second major concern is the widespread use of BADGEs in laboratory environment (e.g., plastic consumables), which often causes background contamination for the trace level analysis (e.g., urine, blood). For example, the analyte backgrounds in sulfatase have been reported in urine analysis (Liu et al. 2019).

Only a few studies have attempted to investigate the environmental and human occurrences of BADGEs and BFDGEs in different sample matrices. The applied analytical methods were summarized in Table 2. For sample preparation, the solid samples (e.g., dust or sewage sludge) were dried and processed by orgaic solvent extraction, followed by purification using solid-phase extraction (SPE). To date, only three studies have investigated its occurrences in indoor dust samples (Liu et al. 2019; Tran et al. 2016; Wang et al. 2012a). For the first two studies, the dust samples were firstly extracted by a combination of water and methanol, and further diluted with 0.2% formic acid in water before being loaded to a Waters MCX cartridge. This acidified environment accelerates the hydrolysis of unstable BADGEs (Lane et al. 2015), which results in low recovery of BADGEs and creates great uncertainty in the absolute quantification. In our previous study (Liu et al. 2019), we found a relatively low recovery (30–50%) of BADGE/BFDGE in the SPE column such as HLB cartridge (Waters) and WCX cartridge (Phenomenex). Therefore, we optimized the clean-up steps using a silica gel cartridge to provide a water-free environment for dust analysis. We found that 10 mL of 20% methanol in ethyl acetate was sufficient for the elution of all tested compounds without a great increase in matrix effect (Liu et al. 2019). The average recovery of BADGE was 76 ± 2%, 71 ± 6% and 88 ± 23% (Average ± S.D) for the dust samples with high, medium and low levels of BADGE spikes. No obvious hydrolysis was observed. All compounds were detected in standard reference material (SRM 2585) except BFDGE-2HCl and BFDGE-2H$_2$O. A good reproducibility of intra-day and inter-day variabilities of all compounds was also observed (1 ~ 25% and 18 ~ 28% for the former and latter, respectively). Therefore, the water-free method for the dry environmental samples is recommended in future studies. It should be noted that the silica gel used was activated by heating at 180 °C overnight, which might result in irreversible adsorption of the epoxides. Therefore, the deactivated silica gel can also be considered for future studies.

Generally, the analysis methods were different among different matrices. For examples, the indoor air samples (particulate phase) were extracted by ethyl acetate (Xue et al. 2016b). The BADGEs in water sample were usually extracted by adding into the tetrahydrofuran dissolved with decanoic acid (Ballesteros-Gómez et al. 2007). While for sludge samples, the freeze-dried samples were first extracted with methanol and then purified by SPE (Xue et al. 2015a). For human biological fluid samples (e.g., urine and blood), one common treatment approach is liquid–liquid extraction using ethyl acetate, followed by a drying process to further concentrate the samples.

As BADGEs are semi-volatile compounds, liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) under multiple reaction mode (MRM) is the most frequently used method to quantify BADGEs in different sample matrices **(see** Table 2**)** (Liu et al. 2019; Tran et al. 2016; Wang et al. 2012b; Wang et al. 2015; Xue et al. 2016b). This method offers good sensitivity and suits for the trace-level quantification. Internal standards d_6-BADGE or d_{10}-BADGE are the most frequently used in the quantification for BADGE and its derivatives. Considering the different physicochemical properties (e.g. much lower estimated log K_{ow} of hydrolysis derivatives) among BADGE and its derivatives, d_6/d_{10}-BADGE may not be the most ideal internal standard for its derivatives. It might be a possible way to fully hydrolyze d_6/d_{10}-BADGE (into d_6/d_{10}-BADGE-2H$_2$O) for future quantification studies. Usually, a reverse-phase column is incorporated with LC-MS/MS for the separation. In electrospray ionization (ESI), BADGEs and BFDGEs are analyzed in positive ionization mode. In terms of the mobile phase, BADGEs and BFDGEs showed a high tendency to form $[M + NH_4]^+$ ion adducts with the mobile phase components. Therefore, the ammonium buffer at 2 mM is often used as a modifier in the mobile phase by enabling the ammonium adducts formation and ensuring signal reproducibility.

6. Occurrences in environmental matrices and human specimen

With the development of above-mentioned analytical methods, this

Table 2
Extraction, purification and analytical methods of BADGEs and BFDGEs in environmental or human samples.

Sample type (Size) Country	Analytes	Limit of Quantification	Sample Amount	Sample Treatment	Separation & Detection[a]	Internal standard	References
Indoor Dust (150 μm) Vietnam	BADGE, BADGE-H_2O, BADGE-$2H_2O$, BADGE-HCl-H_2O	MLOQs: 1 ng/g for BADGEs	200–250 mg	Solid-Liquid Extraction (Methanol: Milli-Q Water 2:1 v/v); Solid phase extraction (Oasis MCX Cartridge)	Betasil C_{18} column (2.1 × 100 mm, 5 μm) serially connected to a Javelin guard column. Methanol (A) and 10% methanol in Milli-Q Water that contained 2 mM ammonium acetate (B)	d_6-BADGE	(Tran et al. 2016)
Indoor Dust (2 mm) U.S., China, Korea, Japan	BADGE, BADGE-H_2O, BADGE-$2H_2O$, BADGE-HCl-H_2O	MLOQs: 0.2 ng/g for BADGEs	100 mg	Solid-Liquid extraction (Methanol: Milli-Q Water 5:3, v/v); Solid phase extraction (Oasis MCX Cartridge)	Betasil C_{18} column (2.1 × 100 mm, 5 μm) serially connected to a Javelin guard column. Methanol (A) and 10% methanol in Milli-Q Water that contained 2 mM ammonium acetate (B)	$^{13}C_{12}$ – BP-3	(Wang et al. 2012a)
Indoor Dust (150 μm)	BADGE, BADGE-H_2O, BADGE-$2H_2O$, BADGE-HCl-H_2O, BADGE-HCl, BFDGE, BFDGE-2HCl, BFDGE $2H_2O$, BADGE-2HCl	MDLs: BADGE (0.103 ng/g), BADGE-H_2O (0.293), BADGE-$2H_2O$ (1.066), BADGE-HCl-H_2O (0.579), BADGE-HCl (0.009), BFDGE (0.274), BFDGE-2HCl (0.065), BFDGE $2H_2O$ (0.055), BADGE-2HCl (N.A.)	50–60 mg	Solid-Liquid Extraction (Methanol) Solid phase extraction (Silica gel cartridge)	Waters Atlantis T3 column (3 μm, 2.1 × 100 mm); Methanol (A) and 10% methanol in Milli-Q Water that contained 2 mM ammonium acetate (B)	d_6-BADGE	(Liu et al. 2019)
Indoor Air (Particulate phase) U.S.	BADGE, BADGE-H_2O, BADGE-$2H_2O$, BADGE-HCl-H_2O, BADGE-HCl, BFDGE, BFDGE-2HCl, BFDGE $2H_2O$	Instrumental LOQs: 0.2 ng/mL for BADGE, BADGE-H_2O, BADGE-$2H_2O$, BADGE-HCl-H_2O, BADGE-HCl ; 1.0 ng/mL for BFDGE and BFDGE-$2H_2O$; 0.5 ng/mL for BFDGE-2HCl.	40 ng	Samples were extracted by ethyl acetate;	Betasil C_{18} column (2.1 × 100 mm, 5 μm) serially connected to a Javelin guard column. Methanol (A) and 10% methanol with 2 mM ammonium acetate (B)	d_6-BADGE	(Xue et al. 2016b)
Human Urine U.S., China	BADGE, BADGE-H_2O, BADGE-$2H_2O$, BADGE-HCl-H_2O	MLOQs: 0.01 ng/mL for BADGE and BADGE-$2H_2O$; 0.02 for BADGE-H_2O; 0.03 for BADGE-HCl-H_2O	500 μL	Deconjucation with β-glucuronidase and sulfatase; Liquid-Liquid Extraction by Ethyl Acetate	Betasil C_{18} column (2.1 × 100 mm, 5 μm) serially connected to a Javelin guard column. Methanol (A) and 10% methanol with 2 mM ammonium acetate (B)	$^{13}C_{12}$ – BP-3	(Wang et al. 2012b)
Human Urine Greece	BADGE, BADGE-H_2O, BADGE-$2H_2O$, BADGE-HCl-H_2O, BADGE-HCl	MLOQs: 0.5 ng/mL for BADGE, BADGE-$2H_2O$; 2 for BADGE-H_2O, BADGE-HCl; 1 for BADGE-HCl-H_2O	500 μL	Deconjucation with β-glucuronidase and sulfatase; Liquid-Liquid Extraction by Ethyl Acetate	Betasil C_{18} column (2.1 × 100 mm, 5 μm) serially connected to a Javelin guard column. Methanol (A) and 10% methanol with 1.5% (w/v) ammonium acetate (B)	$^{2}d_6$-BADGE	(Asimakopoulos et al. 2014a; Asimakopoulos et al. 2014b)
Human Urine Indian	BADGE, BADGE-H_2O, BADGE-$2H_2O$, BADGE-HCl-H_2O, BADGE-HCl, BFDGE, BFDGE-2HCl, BFDGE $2H_2O$	MLOQs: 0.5 ng/mL for BADGE, BADGE-$2H_2O$; 2 for BADGE-H_2O, BADGE-HCl; 1 for BADGE-HCl-H_2O	500 μL	Deconjugation with β-glucuronidase with aryl sulfatase activity; Liquid-Liquid Extraction by ethyl acetate	Betasil C_{18} column (2.1 × 100 mm, 5 μm) serially connected to a Javelin guard column. Methanol (A) and 10% methanol with 1.5% (w/v)	$^{13}C_6$ – BP-3	(Xue et al. 2015b)

(*continued on next page*)

Table 2 (*continued*)

Sample type (Size) Country	Analytes	Limit of Quantification	Sample Amount	Sample Treatment	Separation & Detection[a]	Internal standard	References
					ammonium acetate (B)		
Human Urine Singapore	BADGE, BADGE-H_2O, BADGE-$2H_2O$, BADGE-HCl-H_2O, BADGE-HCl, BFDGE, BFDGE-2HCl, BFDGE $2H_2O$, BADGE-2HCl	MDLs: BADGE (0.014 ng/ml), BADGE-H_2O (0.004), BADGE-$2H_2O$ (0.006), BADGE-HCl-H_2O (0.002), BADGE-HCl (0.003), BFDGE (0.006), BFDGE-2HCl (0.017), BFDGE $2H_2O$ (0.004), BADGE-2HCl (0.017)	5 mL	Deconjugation with β-glucuronidase; Liquid-liquid Extraction by ethyl acetate	Waters Atlantis T3 column (3 μm, 2.1 × 100 mm); Methanol (A) and 10% methanol in Milli-Q Water that contained 2 mM ammonium acetate (B)	d_6-BADGE	(Liu et al. 2019)
Human Blood U.S.	BADGE, BADGE-H_2O, BADGE-$2H_2O$, BADGE-HCl-H_2O, BADGE-HCl, BFDGE, BFDGE-2HCl, BFDGE-$2H_2O$	MLOQs: 0.25 ng/mL for BADGE, BFDGE; 2.5 for BADGE-H_2O, BADGE-HCl-H_2O, BADGE-2HCl; 0.1 for BADGE-$2H_2O$, 1.25 for BADGE-HCl, BFDGE-2HCl, 0.5 for BFDGE-$2H_2O$.	500 μL	Liquid-liquid extraction with ethyl acetate	Betasil C_{18} column (2.1 × 100 mm, 5 μm) serially connected to a Javelin guard column. Methanol (A) and 10% methanol with 2 mM ammonium acetate (B)	d_6-BADGE	(Wang et al. 2015)
Adipose Fat U.S.	BADGE, BADGE-H_2O, BADGE-$2H_2O$, BADGE-HCl-H_2O, BADGE-HCl, BADGE-2HCl, BFDGE, BFDGE-2HCl, BFDGE-$2H_2O$	MLOQs: 0.4 ng/g for BADGE, BFDGE, 4.0 for BADGE-H_2O, BADGE-HCl-H_2O, BADGE-2HCl, 0.16 for BADGE-$2H_2O$, 2.0 for BADGE-HCl, BFDGE-2HCl, 0.8 for BFDGE-$2H_2O$	200–300 mg	Homogenized in a mortar with acetone; concentrated under a gentle nitrogen stream; incubated in ultralow temperature (-20 °C) to separate the lipids from the solvent.	Betasil C_{18} column (2.1 × 100 mm, 5 μm) serially connected to a Javelin guard column. Methanol (A) and 10% methanol with 2 mM ammonium acetate (B)	d_6-BADGE	
Sewage Sludge U.S.	BADGE, BFDGE BADGE-$2H_2O$, BADGE-H_2O, BADGE-HCl-H_2O, BADGE-2HCl, BADGE-HCl, BFDGE-$2H_2O$, BFDGE-2HCl	MLOQs: 2.27 ng/g dw for BADGE, BADGE-H_2O, BADGE-$2H_2O$, BADGE-HCl-H_2O, BADGE-HCl, BFDGE-2HCl. 4.55 ng/g dw for BFDGE, BFDGE-$2H_2O$, BADGE-2HCl	0.1 g	Samples were freeze-dried and extracted with methanol; purified by ENVI-Carb solid phase extraction	Betasil C_{18} column (2.1 × 100 mm, 5 μm) serially connected to a Javelin guard column. Methanol (A) and 10% methanol with 2 mM ammonium acetate (B)	d_6-BADGE	(Xue et al. 2015a)
Wastewater and river water Spain	BADGE BFDGE	MLOQs: BADGE (300 ng/L); BFDGE (450 ng/L)	10.8 mL	Water sample was added in tetrahydrofuran dissolved with decanoic acid. The mixture was stirred and centrifuged.	Hipersil ODS C_{18} column (5 μm, 4.6 mm × 150 mm) Acetonitrile (A) and water (B) Detected by a UV6000LP diode-array detector and a FL3000 fluorescence detector.	N.A.	(Ballesteros-Gómez et al. 2007)
Marine mammals U.S. Coastal Water	BADGE, BADGE-H_2O, BADGE-$2H_2O$, BADGE-HCl-H_2O, BADGE-HCl, BFDGE, BFDGE-2HCl, BFDGE $2H_2O$	Instrumental LOQ (ng/mL): 0.1 for BADGE, BADGE-$2H_2O$, 0.2 for BADGE-HCl, 0.5 for BADGE-H_2O, BADGE-HCl-H_2O, BFDGE-2HCl, 1 for BFDGE, BFDGE-$2H_2O$, 5 for BADGE-2HCl	200–300 mg	Homoginized in a mortar with acetone; washed by 1:1 methanol and acetonitrile; shaken in oscillator and centrifuged.	Betasil C_{18} column (2.1 × 100 mm, 5 μm) serially connected to a Javelin guard column. methanol (A) and 10% methanol with 2 mM ammonium acetate (B)	d_6-BADGE	(Xue and Kannan 2016a)
Wastewater and Sludge U.S.	BADGE, BADGE-H_2O, BADGE-$2H_2O$, BADGE-HCl-H_2O, BADGE-HCl, BFDGE, BFDGE-2HCl, BFDGE $2H_2O$	MLOQs for sludge: 2.27 ng/g dw for BADGE, BADGE-H_2O, BADGE-$2H_2O$, BADGE-HCl-H_2O, BADGE-HCl, BFDGE-2HCl. 4.55 ng/g dw for BFDGE, BFDGE-$2H_2O$, BADGE-2HCl	Waste water: N. A. Sludge: 0.1–0.2 g	**Waste water**: Adjust pH of wastewater samples to 2.5; purified by Strata-X 33 μm Polymeric Reversed Phase (200 mg/ 3 mL); concentrated by nitrogen evaporator. Sludge: Freeze-dried and extracted with 8 mL ethyl acetate and 6 mL methanol; purified by ENVI-Carb solid phase extraction.	Betasil C_{18} column (2.1 × 100 mm, 5 μm) serially connected to a Javelin guard column. Methanol (A) and 10% methanol with 2 mM ammonium acetate (B)	d_6-BADGE	(Xue and Kannan 2019)

[a] Unless stated, the detection method was electrospray triple quadrupole mass spectrometer in multiple reaction monitoring mode (MRM) in positive mode.

section is organized and discussed based on studies reported the occurrences of BADGEs and BFDGEs on different environmental compartments and human, including air, indoor dust, wastewater and sludge, human biological fluids and adipose tissue.

6.1. Occurrence in air and indoor dust

To date, only one study reported the detection of BADGEs and BFDGEs in indoor air (Xue et al. 2016b). In bulk air, BADGE-2H$_2$O (60%) was the main compound in indoor air among all BADGEs (detection rate [DR]: 85.5%), with a concentration as high as 6.71 ng/m^3. The inhalation exposure to BADGE-2H$_2$O for teenagers was estimated as 3.84 ng/kg-bw/day (Xue et al. 2016b). For other BADGEs, BADGE-H$_2$O, BADGE-HCl-H$_2$O and BADGE-HCl were all detected with a median concentration of 0.13 ng/m^3, accounted for 11% of total BADGEs. For BFDGEs, only BFDGE was detected with a median of 0.13 ng/m^3.

The occurrences of BADGEs in indoor house dust have been found in several recent studies from countries including the U.S., China, Korea, Singapore, Japan, and Vietnam **(**Table 3**)**. For all four countries, the general distribution profiles of BADGEs in dust samples are quite similar, with BADGE-2H$_2$O and BADGE-HCl-H$_2$O as the predominant ones. Similarly, the hydrolysis compound BADGE-2H$_2$O was found with the highest median concentrations of 1,920 ng/g in Korea, followed by Japan, the U.S., and China. The estimated daily intake (EDI) of BADGEs via dust ingestion is 6.5 ng/kg-bw/day. In Vietnam (Tran et al. 2016), the concentrations of total BADGEs in indoor dust range from 23 to 1,750 ng/g (median 184 ng/g) and the EDI range from 0.158 to 0.736 ng/kg-bw/day. Among four tested BADGEs, BADGE-2H$_2$O (accounted for 72%) was the predominant compounds found in the dust, followed by BADGE-H$_2$O (16%), whereas the percentage of BADGE-H$_2$O only accounted for < 2% to 5% in other studies.

As seen in Fig. 2**a**, in our study using a water-free method (Liu et al. 2019), BADGE-2H$_2$O was also found as the dominant compound, ranging from 214 to 35,419 ng/g with a GM concentration of 1,843 ng/g in the dust from Singapore. The contribution of BADGE-2H$_2$O to total BADGEs ranged from 34% to 96% with an average of 61%. Besides BADGE-2H$_2$O, BADGE-2HCl concentration in dust samples ranged from < 56 to 2,474 ng/g, with a GM concentration of 223 ng/g (Liu et al. 2019). In terms of BADGE-2HCl concentration in total BADGEs, the value ranged from 0 to 49%, with an average of 17%. Another transformation product BADGE-HCl-H$_2$O was also detected with concentration ranging from 66 to 1,832 ng/g and a GM of 233 ng/g. As BADGE chlorinated compounds were not tested in previous studies, we revealed a slightly different distribution profiles of all BADGEs in indoor dust **(**Fig. 2**b).** For example, it was found that BADGE-2HCl accounted for approximately 17% of total BADGE concentrations. It should be noted that the dust samples collected in Singapore were all from households while the earlier mentioned studies (Tran et al. 2016; Wang et al. 2012a) also included those from supermarkets, laboratories etc.

The concentration of another parent compound BFDGE in dust samples (DR: 44%) range from < 4.9 to 421 ng/g with a GM concentration of 2.5 ng/g, which is one order of magnitude less than BADGE (Liu et al. 2019). BFDGE-2H$_2$O concentration in dust samples range from < 0.055 to 130.0 ng/g with a GM concentration of 0.3 ng/g, while BFDGE-2HCl was only detected in one sample with concentration of 903.2 ng/g **(**Table 3**).** In contrast to BADGEs, the parental BFDGE was dominant (average relative contribution > 50%) in 12 of 17 dust samples where BFDGEs were detected, suggesting that the environmental transformation of BFDGE may not be as rapid as BADGE.

In this review, we also compared the occurrence of total BADGEs (Liu et al. 2019; Tran et al. 2016; Wang et al. 2012a) with other common bisphenol plasticizers (Dong et al. 2019; Liu et al. 2019; Tran et al. 2016; Wang et al. 2012a). As shown in Fig. 2**c**, the most abundant bisphenol plasticizers were BPA (1.48 ± 1.19 μg/g) and total BADGEs (1.52 ± 0.81 μg/g), which was followed by BPS (0.33 ± 0.27 μg/g) and bisphenol F (0.12 ± 0.16 μg/g). The detected mean concentrations of other bisphenol analogues were generally lower, all of which were <0.002 μg/g.

6.2. BADGEs in wastewater and sludge

To date, there are very few studies reported the level of BADGEs in wastewater and sludge. BADGEs and BFDGEs were determined in wastewater samples (n = 4) and river water samples (n = 3) collected from Spain (Ballesteros-Gómez et al. 2007). None of the targeted compounds was detected in river water samples **(**Table 3**)**. In contrast, BADGE was detected in all wastewater treatment plant (WWTP) influent samples, with the concentration ranging from 0.57 ± 0.04 ~ 1.15 ± 0.1 μg/L. BFDGE was also detected in two WWTP influent samples, with the concentration ranging from non-detected to 0.41 ± 0.06 μg/L. In another study, BADGE and its hydrolysis compounds, as well as BADGE-HCl-H$_2$O, were detected in wastewater samples from two WWTPs in the Albany area of New York State, U.S. BADGE-2H$_2$O was the predominant compound and its GM concentrations in influents was 4.36 ng/L. BADGE-HCl-H$_2$O was the second most abundant chemical found at a GM concentration of 1.72 ng/L (Xue et al. 2019). Sludge is usually the sink of hydrophobic SVOCs. BADGE, BFDGE and eight of their derivatives were determined in archived biosolid samples collected from 68 WWTPs in the U.S. (Xue et al. 2015a). Expectedly **(**Fig. 2**b)**, BADGE-2H$_2$O was the most frequently detected chemical (DR: 99%), with the highest abundance (median: 93.6 ng/g dry weight) among these compounds (Xue et al. 2015a). In summary, we can draw the conclusion that BADGEs are quite ubiquitous chemicals in the environment.

6.3. BADGEs detected in human biological fluids and adipose tissue

The occurrences of BADGEs have been found in human urine samples collected from the U.S., China, Singapore, Greece and India. In the urine samples collected from the U.S. and China, BADGE-2H$_2$O was the predominant compound, accounting for 45–60% of the total BADGEs concentration, followed by BADGE (17–24%) (Wang et al. 2012b). The urinary concentrations of total BADGEs in the U.S. ranged from 1.24 to 9.03 ng/mL, with a GM concentration of 3 ng/mL. The urinary concentrations of total BADGEs from adults (GM: 1.36 ng/mL) and children (1.02 ng/mL) in China were 3-fold lower than those found in the U.S.. In another study, the occurrence of five BADGE-related compounds, BADGE, BADGE-H$_2$O, BADGE-2H$_2$O, BADGE-HCl-H$_2$O and BADGE-HCl, were found in Greece (Asimakopoulos et al. 2014a), with the urinary concentrations of total BADGEs from 0.3 to 20.9 (GM: 0.9) ng/mL. Similarly, in another study that investigated the urinary BADGEs and BFDGEs for Indian children (Xue et al. 2015b), BADGE and BADGE-2H$_2$O were the predominant compounds among all the analytes. The GM urinary concentrations of BADGE-2H$_2$O and BADGE in Indian children were 12.2 and 24.8 ng/mL, respectively, which were one order of magnitude higher than those reported for Chinese children (0.594 and 0.175 ng/mL). In another study conducted in Singapore (Liu et al. 2019), total BADGEs were detected in 50% of the urine samples, ranging from < 0.016 to 0.889 ng/mL with a GM concentration of 0.03 ng/mL (Liu et al. 2019; Xue and Kannan 2016a), which was lower than those found in the U.S. (GM: 1.010 ng/mL), China (GM: 1.073 ~ 1.328 ng/mL) (Wang et al. 2012b) and Greece (GM: 0.900 ng/mL) (Asimakopoulos et al. 2014a). Total BFDGEs were only detected in 5 urine samples, ranged from < 0.65 to 1.733 ng/mL.

The urinary total BADGEs level was also compared with other bisphenol analogues as shown in Fig. 2**c**. In line with the dust results, BPA and BADGE were dominant in human urine samples. Among them, BPA was the most abundant one, with a median concentration of 2.1 ± 0.4 ng/mL (CDC 2018). The urinary concentration of total BADGEs (1.08 ± 0.82 ng/mL) was slightly lower than BPA. Similar to dust samples, BADGE level was approximately 2-fold higher than BPS (0.43 ± 0.06) ng/mL but both were lower than BPA in urine samples **(**Fig. 2**c)**.

BADGE, BFDGE and seven of their derivatives were also determined

Table 3
The concentrations of BADGEs and BFDGEs in different sample matrices collected from different countries.

Samples	Country	Median (Range)									Ref.
		BADGE	BADGE-H_2O	BADGE-H_2O-HCl	BADGE-2H_2O	BADGE-HCl	BADGE-2HCl	BFDGE	BFDGE-2H_2O	BFDGE-2HCl	
Environmental Matrices											
Indoor Dust (ng/g)	U.S. (n = 40)	2.40 (<0.2[b]-12)	27 (0.700–486)	127 (14–2,260)	1,110 (51–29,800)	N.A.	N.A.	N.A.	N.A.	N.A.	(Wang et al. 2012a)
	China (n = 55)	51 (0.9–7,750)	67 (2–8,850)	124 (5–1,720)	1,074 (35–38,300)	N.A.	N.A.	N.A.	N.A.	N.A.	
	Korea (n = 41)	18 (0.1–98)	91 (3.9–2,440)	270 (56–13,100)	1,920 (564–30,500)	N.A.	N.A.	N.A.	N.A.	N.A.	
	Japan (n = 22)	2.600 (<0.2–8.21)	27 (<0.2–421)	267 (56–24,300)	1,410 (291–59,900)	N.A.	N.A.	N.A.	N.A.	N.A.	
	Singapore (n = 33)[a]	16 (<0.1–690)	93 (18–450)	233 (<0.579–1,832)	1,843 (214–35,419)	3 (<0.01–480)	223 (<0.53–2,474)	2.5 (<0.27–421)	0.27 (<0.06–130)	0.04 (<0.07–2473)	(Liu et al. 2019)
	Vietnam (n = 46)	11.100 (<1–172)	28 (1.79–255)	11.400 (<1–417)	129 (7.58–1,630)	N.A.	N.A.	N.A.	N.A.	N.A.	(Tran et al. 2016)
Air (ng/m^3) bulk air	U.S. (n = 83)	0.07 (<MLOQ-2.54)	0.13 (<MLOQ-2.54)	0.13 (<MLOQ-1.62)	0.7 (<MLOQ-6.71)	0.13 (<MLOQ-0.52)	n.d.	0.13 (<MLOQ-0.52)	n.d.	n.d.	(Xue et al. 2016b)
Wastewater (ng/L)[e]	U.S. (n = 2) [a]	Influent: <2.27–4.95 Effluent:<2.27–6.2	n.d.	Influent: <2.27–34.0 Effluent: <2.27–3.52	Influent: <2.27–673 Effluent: <2.27–208	N.A.	N.A.	N.A.	N.A.	N.A.	(Xue and Kannan 2019)
	Spain (n = 4)	Influent :0.57–1.15 Effluent: n.d.	N.A.	N.A.	N.A.	N.A.	N.A.	Influent :n.d.-0.41 Effluent: n.d.	N.A.	N.A.	(Ballesteros-Gómez et al. 2007)
River Water (ng/mL)	Spain (n = 3)	n.d.	N.A.	N.A.	N.A.	N.A.	N.A.	n.d.	N.A.	N.A.	
Sludge (ng/g dry weight)	U.S. (n = 84)	9.66 (<0.5–1,980)	<2 (<2–2,090)	3.66 (<1–121)	93.6 (<2–2,290)	<2.27 (<2.27–112)	<4.55 (<4.55–37.5)	<4.55 (<4.55–126)	<4.55 (<4.55–101)	<2.27 (<2.27–19.1)	(Xue et al. 2015b)
Products											
Dental Sealants (μg/g)	U.S.(n = 70)	0.29[a]	1.43	2.76	13.7	0.35	1.94	N.A.	N.A.	N.A.	(Xue et al. 2018)
Textiles (ng/g)	U.S. (n = 77)	0.23 (<0.74–4.37)	N.A.	2.88 (<1.47–62.9)	0.82 (<1.47–13.1)	N.A.	N.A.	13.6 (<1.47–132)	N.A.	N.A.	(Xue et al. 2017)
Human Specimens											
Urine (ng/mL)	U.S. (n = 31)	0.68 (0.15–2.23)	0.42 (0.12–1.36)	0.31 (<0.03–3.41)	1.08 (0.15–4.60)	N.A.	N.A.	N.A.	N.A.	N.A.	(Wang et al. 2012b)
	China (Adult; n = 26)	0.24 (0.04–0.71)	0.25 (0.03–1.67)	0.11 (<0.03–0.35)	0.63 (0.23–2.19)	N.A.	N.A.	N.A.	N.A.	N.A.	
	China (Children; n = 70)	0.18 (0.08–1.23)	0.14 (<0.02–0.36)	0.10 (<0.03–1.34)	0.55 (0.33–5.82)	N.A.	N.A.	N.A.	N.A.	N.A.	
	Greece (n = 100)	<0.5 (<0.5–0.60)	<2 (<2–3.7)	<1 (<1)	0.60 (<0.5–18.70)	N.A.	N.A.	N.A.	N.A.	N.A.	(Asimakopoulos et al. 2014a)
	Singapore (n = 32) [a]	0.0076 (<0.01–0.1)	0.0022 (<0.004–0.05)	0.0052 (<0.002–0.56)	0.0032 (<0.006–0.3)	0.0018 (<0.003–0.05)	n.d. (<0.017)	0.0032 (<0.006–0.02)	0.0026 (<0.004–0.06)	0.0122 (<0.017–1.71)	(Liu et al. 2019)
	Indian (Children; n = 76)	24.80[a] (0.07–295)	N.A.	N.A.	12.20 (0.07–1,450)	N.A.	N.A.	N.A.	N.A.	N.A.	(Xue et al. 2015b)
Blood (ng/mL)	U.S. (n = 20)	<0.25 (<0.25)	2.26 (<2.5–9.54)	<2.5 (<2.5–1.41)	7.15 (<0.1–65.1)	<2.5 (<2.5)	<2.5 (<2.5)	56.2 (<23.3–180)	<0.5 (<0.5–6.65)	<1.25 (<1.25)	(Wang et al. 2015)
Adipose (ng/g wet weight)	U.S. (n = 20)	<0.4 (<0.4–5.16)	<4 (<4–4.33)	<4 (<4–28.2)	3.44 (<0.16–45.4)	<2.0 (<2.0–7.20)	<4.0 (<4.0–3.11)	178 (<19.1–4,500)	<0.8 (<0.8–5.20)	5.65 (<2.0–20.9)	

[c] *N.A.* = Not available
[d] *n.d.* = Not detected
[a] Only geometric mean (GM) value is available from these studies.
[b] *LOQ* = Limit of Quantitation
[e] Only range was available for wastewater samples.

in a few human adipose fat and blood plasma samples collected from New York City, U.S. (Wang et al. 2015). Similar to the urinary distribution profile, BADGE-2H$_2$O was predominant and detected in 60% and 70% of the adipose and plasma samples, respectively. High concentrations and detection frequencies of BFDGE were also found in both adipose (19.1 ~ 4,500 ng/g) and plasma samples (23.3 ~ 180 ng/g). The occurrence and bioaccumulation of BADGEs or BFDGEs were also examined in 121 tissue samples (including liver, kidney, blubber, and brain) from eight species of marine mammals collected from the U.S. coastal waters of Florida, California, Washington, and Alaska (Xue and Kannan 2016a). Among all tested compounds, BADGE-HCl was detected in 78.5% of the samples, at concentrations of up to 2,950 ng/g (wet weight). The favourable organ of BADGEs accumulation was livers, but considerable concentrations of BADGE-2HCl also occurred in brains and kidneys.

In this review, we also compared the concentration ratio profiles of BADGEs in products, environmental samples and human specimens as seen in Fig. 2**b**. In products, the relative percentage of unstable BADGE derivatives such as BADGE-HCl-H$_2$O (77% for textile; 15% for dental sealants) accounted for relatively higher portion compared with those values in the environmental samples (6% in air; 3.4% in sludge; 10% for dust). The relative percentage of BADGE-HCl-H$_2$O was also lower in human specimens such as urine (11%), blood (0%) and adipose fat (0%). It should be noted that the relative percentage of BADGE in sludge (9%), wastewater (10.6%) and urine (34%) were relatively high, though the exact reason is not clear yet. For sludge or wastewater, it is possible that the adsorption of BADGE to these samples may affect its half-lives of hydrolysis. While regarding the high percentage of BADGE in urine samples, this might due to the relatively short biological half-lives in human.

7. Abiotic and biotransformation of BADGE

Since BADGEs showed the widespread occurrences on environmental/human samples, it is important to get a full picture of its transformation pathway. Owing to the reactivity of BADGE, it can be transformed into other compounds via hydrolysis and enzymatic reactions with other small molecules with and without enzyme involvement. Hereby, we summarized the transformation of BADGE under abiotic and biotic conditions.

7.1. BADGE stability and abiotic transformation

We have previously tested the stability of BADGEs by monitoring their hydrolysis products (BADGE-H$_2$O, BADGE-2H$_2$O, BFDGE-2H$_2$O) at pH = 7 and 25 °C (Liu et al. 2019). A steady decay of BADGE and an increase of BADGE-H$_2$O and BADGE-2H$_2$O were observed in the hydrolysis process, and BFDGE was also observed with the same trend in our study. The half-lives of BADGE and BFDGE were approximately 3 days, which are close to 2 days as estimated in an earlier study (Lane et al. 2015).

Fast degradation of BADGE was observed in protein-rich and carbohydrate-rich food products (Richard et al. 1999). AAn earlier study has reported its 'disappearance' in food packaging materials, which resulted from its reaction with food components such as protein and amino acids (Petersen et al. 2008). As shown in Fig. 3**a**, adduct formation was observed in the side chains of N-protected derivatives of cysteine, tyrosine, lysine, histidine and methionine (Petersen et al. 2008). BADGE also reacts with peptides and proteins in foods. Cysteine was the predominant reaction center for amino acids, peptides and protein (Coulier et al. 2010). Considering the high reactivity of BADGE, its metabolism may be much more complicated.

7.2. Biotransformation

Although metabolism is one of the important detoxification strategies in organisms (Kluger et al. 2013), the bioactivity profiles of biotransformed products can sometimes cause more adverse and toxic effects (Kirchmair et al. 2013). Comparing with BPA, much less information is available for BADGEs' metabolisms and toxicities. The degrees of their toxicity are believed to depend mainly on the fractional concentrations of unreacted epoxy groups (Suárez et al. 2000). Until now, very few studies have documented the metabolism of BADGE and its main metabolites were presumed to be the hydrolysis products (Wang

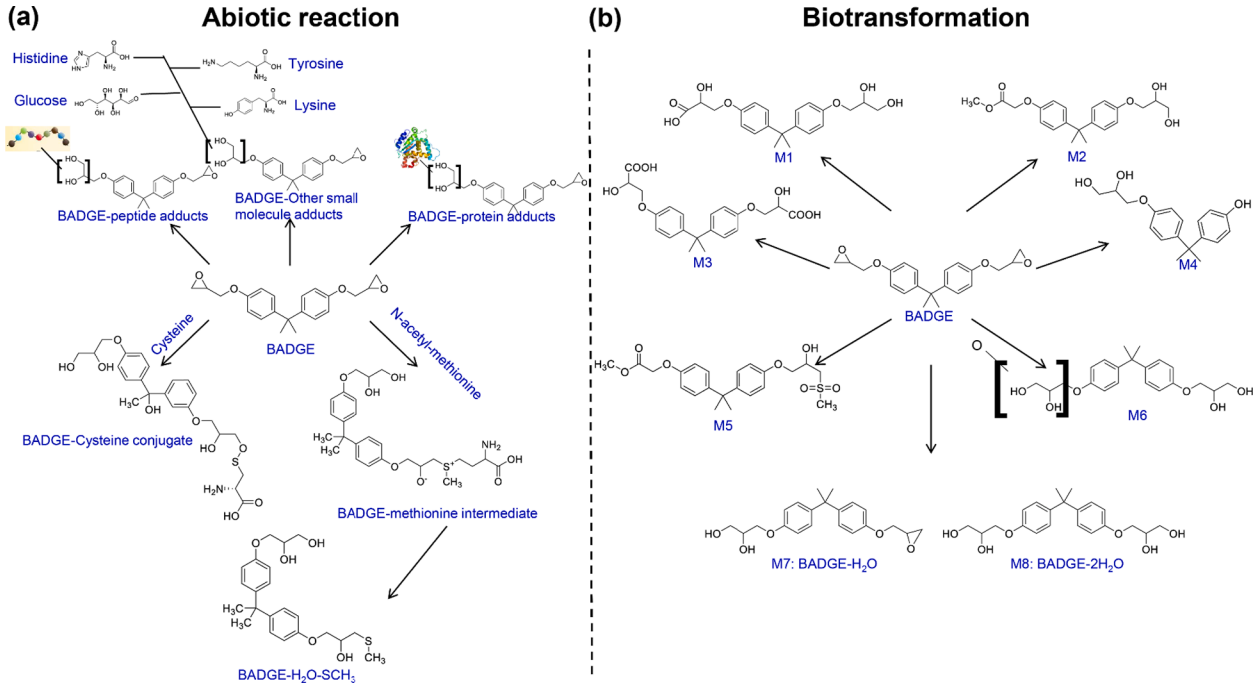


Fig. 3. (a) Abiotic reaction of BADGE with amino acids and other food ingredients reported in earlier studies (Coulier et al. 2010; Petersen et al. 2008); (b) biotransformation of BADGE in Male Fischer 344 Rats (Probe; M1 to ~ M5) (Nolan et al. 1981) and *in vitro* human liver (M1, M6, M7 and M8) (Vervliet et al. 2020).

et al. 2012b). In an *in vivo* study, a dose of 2.7 mg/kg-bw of 2-^{14}C-propane-labelled BADGE was given orally to F344 rats. The results showed that less than10% of BADGE in plasma was unchanged (Nolan et al. 1981). The major identified metabolites (M1 to ~ M5) were shown in Fig. 3**b**. It should be noted that the formation of methylthio- or methylsulphinyl-compounds (M2 and M5) is uncommon and it is possible that M2 and M5 may be oxidative artifacts of the corresponding methylthio methylthio- or methylsulphinyl-compounds. In another mouse study, the bis-diol of BADGE (i.e., BADGE-2H_2O) was excreted in both free and conjugated forms in total amounts representing 5% of the original dose (Climie et al. 1981). Both studies suggested that a large proportion of parent compound has been bio-transformed to some unknown metabolites. In addition, the biotransformation mechanism can be quite complex considering the reactivity of epoxides that can react with many nucleophile species. Therefore, the potential bioactivation of BADGE is warranted for further investigation. To date, the biological half-lives of BADGE and its derivatives in human is yet unknown and also warranted for further studies.

Another recent study identified the phase I *in vitro* biotransformation products of BADGE and BFDGE using human liver microsomes (Vervliet et al. 2020). During incubation with microsomal fractions, the epoxides of BADGE were rapidly hydrolyzed in an NADPH-independent manner, resulting in the formation of BADGE-H_2O and BADGE-2H_2O **(M7 and M8 in** Fig. 3**b)**. Furthermore, BADGE can also undergo oxidative reactions (e.g. hydroxylation and carboxylation), generated BADGE-2H_2O-OH (M6) and BADGE-H_2O-COOH (M1) as shown in Fig. 3**b**; respectively. The *in vitro* biotransformation of BFDGE is similar to BADGE as it can also form hydrolysis product BFDGE-2H_2O in an NADPH-independent manner. The further oxidation of BFDGE-2H_2O led to the newly reported carboxylic acid, BFDGE-H_2O-COOH (Similar to M1).

8. Toxicity

Considering the widespread occurrences and reactivity of BADGEs, it is demanding to systematically review its toxic effects. This section is organized to review both *in vitro* and *in vivo* toxicological studies of BADGEs and BFDGEs.

8.1. *In vitro* toxicological studies

In vitro bioassays reported that BADGEs exhibit endocrine-disrupting potentials as well as mutagenicity, genotoxicity and cytotoxicity (Ramilo et al. 2006; Suárez et al. 2000; Sueiro et al. 2006) as seen in Fig. 4. Regarding endocrine-disrupting potentials, BADGE and its derivatives exhibit anti-androgenic and estrogenic effects as well as obesogenic properties. For instance, the chlorohydroxy derivatives of BADGE and BFDGE (i.e., BADGE-2HCl and BFDGE-2HCl) can act as an androgen antagonist through the process of binding to the androgen receptor in CHO-K1 cell lines (Satoh et al. 2004). Additionally, BADGE, BADGE-2H_2O and BADGE-2HCl induced proliferation of breast cancer (T47D) cell at concentrations of 10^{-14}-10^{-4} M, while did not bind to estrogen receptor (ERα) in the binding assay (Nakazawa et al. 2002). Some studies have investigated the obesogenic properties of BADGE and suggested these cellular processes may be cell-type specific. For example, BADGE was shown to be an antagonist of PPARγ in the 3 T3-L1 and 3 T3-F442A cells (Wright et al. 2000). In contrast, BADGE also exhibits PPARγ agonistic activities in the ECV403 cell line (Bishop-Bailey et al. 2000). Although BADGE was considered as a low-affinity ligand that required very high concentrations to demonstrate PPARγ antagonism with half-maximal inhibitory concentration [IC_{50}] of approximately 100 μM. A study revealed its ability to induce adipogenic differentiation in both mesenchymal stromal stem cells (MSCs) and preadipocytes at low nanomolar concentrations (Fehlberg et al. 2002). In a recent study, researchers evaluated the direct effects of the bisphenols on Ca^{2+} signaling in human sperm cells through a Ca^{2+} fluorimetric assay. The results showed that 10 μM BADGE can induce Ca^{2+} signals, which almost completely abolished using the effect of CatSper inhibitor RU1968 in human sperm cells. The results suggested that bisphenols such as BADGE can affect Ca^{2+} signaling in human sperm cells through activation of CatSper (Rehfeld et al. 2020).

In addition to its endocrine-disrupting potentials, many *in vitro* endpoints screening tests suggested BADGEs exhibit genotoxicity and mutagenicity. For example, a study has reported the increase in the frequency of chromosomal aberration as well as the percentage of cells with chromatid gaps and chromatid exchanges figures in rat liver cells exposed to 3.75–15 μg/mL of BADGE (EPA, 1981). In another study, a toxicological screening assay micronucleus test (MNT) was conducted to

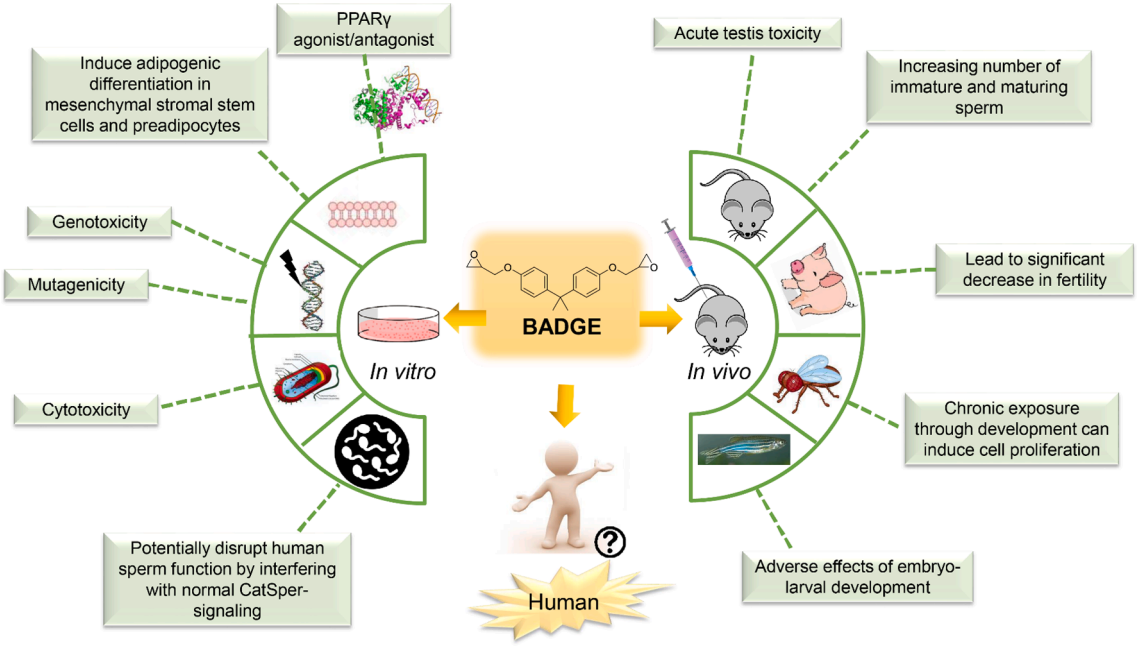


Fig. 4. *In vitro* and *in vivo* toxicity summary of BADGE.

examine the genotoxicity of BADGE, BADGE-H_2O, BADGE-$2H_2O$ and BADGE-2HCl to human peripheral blood lymphocytes in the presence or absence of an exogenous metabolizing system S9 rat liver (Suárez et al. 2000). The results suggested that all tested chemicals are able to induce both cytotoxic and genotoxic effects, but their triggered effects are different. The genotoxicity of BADGE is stronger than its hydrolysis products BADGE-H_2O and BADGE-$2H_2O$ while the genotoxicity of BADGE-2HCl is comparable to BADGE-H_2O. A study has also reported the ability of BADGE and BADGE-H_2O to cause genetic alterations using *Escherichia coli* tryptophan reverse mutation test with strains WP2, WP2uvrA and IC3327 (Sueiro et al. 2006). These results suggested these compounds can induce mutagenic effects in strains WP2uvrA and IC3327.

BADGEs were also able to induce *in vitro* overt cytotoxicity at a specific dose. Ramilo et al. (2006) reported that BADGE and BFDGE can induce morphological changes and cell detachment from the substratum

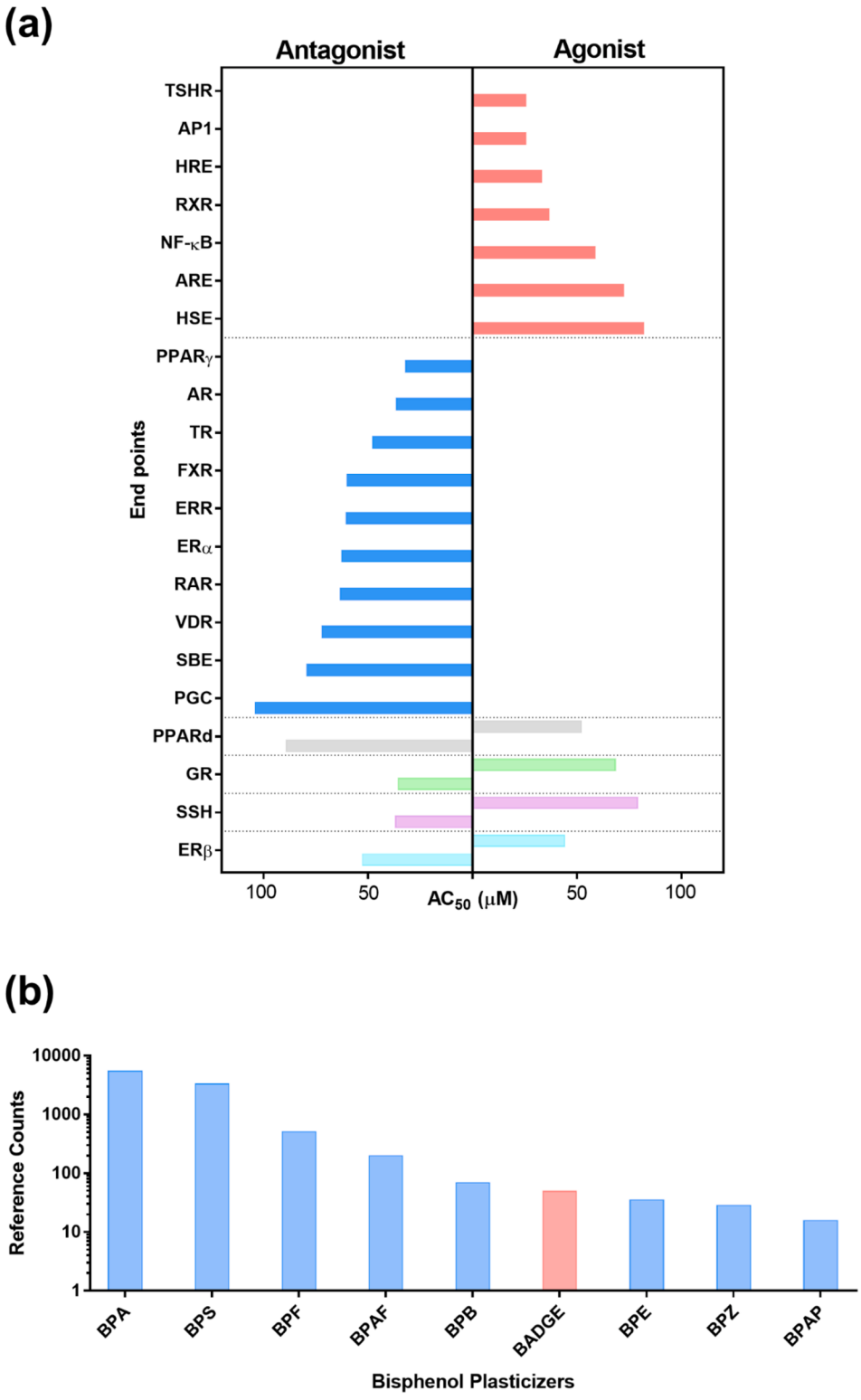


Fig. 5. (a) *In vitro* Toxicity summary of BADGE according to the active assay results from EPA ToxCast database and their potency AC_{50}; (b) The reference counts of studies on occurrences, human exposure and toxicity of different bisphenol analogues. [Abbreviations: TSHR (Thyroid stimulating hormone receptor); AP1 (Activator protein 1); HRE (Hormone response element); RXR (Retinoid X receptor); NF-κB (Nuclear factor- κB); HSE (Heat shock factor protein); PPARγ/d (peroxisome proliferator-activated receptor); AR (Androgen receptor); TR (Thyroid hormone); FXR (Farnesoid X receptor); ERR , ERβ or ER α (Estrogen receptor); RAR (Retinoic acid receptor); VDR (Vitamin D receptor); SBE (Smad binding element); PGC (Progastricsin); GR (Glucocorticoid receptor); SSH (Sonic hedgehog)].

and inhibit cell proliferation of human epithelial colorectal adenocarcinoma (Caco-2) Cell. Moreover, they found that both chemicals at 200 μM can induce F-actin depolymerization and the effects are potent after 24 h of incubation. A newly published study examined the toxicity, endocrine and lipid disruption potentials of BADGE, BADGE-H_2O and BADGE-2HCl in human placental cells (Marqueño et al. 2019). In general, BADGE-2HCl and BADGE showed higher cytotoxicity than BADGE-H_2O. Additionally, BADGE-2HCl altered the cell lipidome by decreasing the amount of neutral lipids, while exposure to BADGE increased the intracellular concentration of triacylglycerides (Marqueño et al. 2019).

We further systematically evaluated the *in vitro* toxicity of BADGEs by mining the results from the U.S. EPA Toxicity Forecaster (ToxCast) (U.S.EPA, 2015). The active results from those bioassays integrated with their potency half-maximal activity concentrations (AC_{50}) are shown in Fig. 5**a**. Overall, BADGE is able to demonstrate antagonism or agonism for many receptors such as estrogen receptor (ER), peroxisome proliferator-activated receptor (PPAR) and glucocorticoid receptor (GR). BADGE was also found to be an antagonist of androgen receptor, which is in agreement with the observed anti-androgenic effect in an earlier study (Satoh et al. 2004). In addition, the ability of BADGE to demonstrate antagonism of PPARγ was also consistent with a previous study (Wright et al. 2000).

8.2. *In vivo* toxicological studies

In this review, we have summarized the *in vivo* toxicity results in Fig. 4. The *in vivo* systemic toxicity of BADGE has been examined as early as 1958 for both single-dose and full-dose tests (Hine et al. 1958). In the single-dose oral toxicity test, a median lethal dose (LD_{50}) of BADGE was higher than 1,000 mg/kg, which was recorded in studies with rats, mice, and rabbits. In the full-dose test, the oral LD_{50} for a commercial BADGE-based epoxy resin was reported to be 11,400 mg/kg in rats, 15,600 mg/kg in mice, and 19,800 mg/kg in rabbits.

In addition to the acute oral toxicity, accumulated *in vivo* evidence suggested BADGE can seriously damage the reproductive systems and endocrine systems in pigs, rats and native amphibian species. For example, a study found the plastic bags used for semen storage led to a significant decrease in fertility for a group of pig farms (Nerin et al. 2014). The main causal compound responsible for the failures was likely due to BADGE as an adhesive used to manufacture the multilayer plastic bags. Additionally, they also found a synergistic reproductive toxicity effect developed between BADGE, its derivatives, and the cyclic lactone. Another study investigated the developmental effects of prenatal and postnatal exposures to BADGE at 375 mg/kg/day orally in male rat offsprings (Hyoung et al. 2007). Their body weight and relative organ weight (including lung, adrenal gland, epididymis, prostate, spleen testis, and brain) have changed in 6 or 9 weeks, and the testicular toxicity appeared in 9 weeks. BADGE also exhibits acute testis toxicity for male rats (Yang et al. 2010). This study found an increasing number of immature and maturing sperm on the testis when the male rats were exposed to the single-dose of BADGE at 750; 1,000 and 2,000 mg/kg/day. However, if below 1,000 mg/kg/day, no significant difference between the treatment group and control group was observed with respect to sperm count, headcount, motility and abnormality. In addition, BADGE has been reported to have adverse effects on *Rhinella arenarum* in an embryo-larval development study through standardized bioassays (Wolkowicz et al. 2016). The results showed that BADGE was more toxic to embryos (96 h post-fertilization with median lethal concentrations: 0.04 mg/L) than to larvae (2.2 mg/L) at all exposure times. Significant lethality rates were also observed for embryos and larvae when exposed to 0.0005 mg/L and 10 mg/L of BADGE, respectively. In a recent study, the biological effect of BADGE during development was investigated using *Drosophila*. Through whole transcriptome sequencing, differentially expressed genes (DEG) of *Drosophila* after raising on food containing BADGE were enriched in regulating cell proliferation, including DNA replication and cell cycle control. Furthermore, raising larvae on BADGE-containing food induced hemocyte (blood cell) over-proliferation. Chronic exposure to the BADGE through development can also induce cell proliferation (Williams et al. 2020).

In summary, the toxicological information and mechanism are still quite limited for BADGE and its derivatives, though the results from a few endpoints suggested they can be potential endocrine disruptors. More future studies should be conducted to identify the primary mode of action of BADGEs. In addition, very little information is available for the *in vitro* or *in vivo* toxicity at the environmentally or human-relevant levels. In one of our previous studies, we have estimated the relative contribution of BADGE among 23 common environmental chemicals. Tthe results showed that BADGE is not that potent as BPA in inducing metabolic changes to MCF-7 cells (Liu et al. 2020). The chemical interactions between BADGE and 12 other xenobiotics were also evaluated. BADGE was found to be more likely to generate antagonist effect with other chemicals. For examples, the coexposure of BADGE with parabens compromised their cytotoxicity potency on the HepG2 cell line (Zhang et al. 2020).

9. Conclusion and future studies

As shown in this review, the production volume or environmental/human occurrences of BADGEs are similar to or even higher than other major bisphenol chemicals such as BPS. However, to date, there are still quite limited studies on investigating these compounds in different environmental matrices. BPA and BPS were generally very well-studied while very few studies focused on BADGE (~50) (Fig. 5b). Additionally, due to the widespread applications of BADGEs in products and limited monitoring data, it is yet not clear of which exposure pathway (e.g. dietary intake, dust ingestion or inhalation exposure) is more important to the entire human exposure. More future environmental monitoring works are warranted. It is worth noting that a water-free method should be considered during sampling and pretreatment processes to minimize the loss of parent BADGE and its unstable derivatives. Considering the different physicochemical properties among BADGEs, it might be a way to hydrolyze d_6/d_{10}-BADGE (into BADGE-$2H_2O$) as the internal standard for quantification of its derivatives in the future. In addition, as a reactive chemical, the migration and emission of BADGE from the products have not been characterized yet. Comparing with most non-binding chemical additives such as BPA and flame retardants, which can be well predicted using the classic partitioning equilibrium in the environmental and human condition Therefore, the study on the fate of reactive BADGEs is still lacking.

Another knowledge gap is lying with this question: what are the implications of BADGEs' reactivity on their transformation and toxicity? To date, very few studies have investigated the biotransformation of BADGE, as summarized above. The identification of these reactive compounds in the organism is more challenging than some other traditional xenobiotics due to many unknown rules. Both abiotic and biotic transformation pathways exist for BADGEs. To date, the biological half-lives of BADGE and its derivatives in human are yet unknown and warranted for further studies. In addition, a feasible and robust discovery platform is needed to assist with the identification of the potential metabolites of reactive BADGEs. A fully understanding of their metabolic pathways will provide a more comprehensive view on the assessment of their toxicity and potential health consequences as well as some information on the choice of the suitable biomarker for BADGE exposure. It is a fact that BADGE-$2H_2O$ can be readily detected in human urine. However, some BADGE-$2H_2O$ has already been formed in the environment. According to the previous studies, it is likely that BADGE showed a much higher risk than its hydrolysis products. Therefore, BADGE-$2H_2O$ might not be a good biomarker to estimate the potential risk of BADGE, considering its pre-existence in the environment. The protein adduct formed by BADGE is also a great concern for human health. Considering their reactivity and covalent protein binding potentials with amino acid residues such as cysteine or methionine, the

roles of BADGEs in mediating the activity of proteins may be very important. However, very little information is available for the protein targets of BADGEs. Future studies using chemical proteomics methods such as Activity-Based Protein Profiling (ABPP) and Cellular Thermal Shift Assay (CESTA) (Cravatt et al. 2008; Molina et al. 2013; Xu et al. 2021a; Xu et al. 2020; Xu et al. 2021b) can be considered to identify the global protein targets of BADGEs and their associated biological consequences.

Comparing with BPA and other common plastic additives, the toxicology information of BADGEs is still very limited. The endocrine disruptive effect of BADGE remains unknown, which could be one of the major focuses in the future. It is still not clear whether its PPARγ antagonistic effect is the main driver for its toxicological mechanism. A systematic approach (e.g., omics) should be employed to study its global impact on the biological pathways and compare the toxicity between them and other plastic additives with similar structures.

In summary, BADGEs are a group of compounds that are worthy to pay attention. Their potential health concerns are still not clear. More importantly, it can act as a classical model chemical to study the biological fate of reactive chemicals, further broadening our knowledge and filling the gaps on the analytical method, occurrence, transformation and toxicity of those "versatile" compounds.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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