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Review

# Analytical methods for the determination of mixtures of bisphenols and derivatives in human and environmental exposure sources and biological fluids. A review

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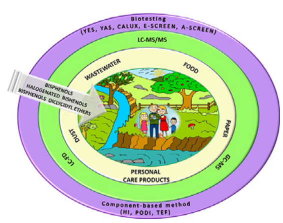
## HIGHLIGHTS

- Analytical methods for the (bio) monitoring of mixtures of bisphenols are reviewed.
- LC and CG coupled to MS are the preferred techniques.
- Method-dependent sample treatments are required to remove matrix effects.
- Toxicity is evaluated in terms of receptor activation, cell proliferation and physiological responses.
- Simpler, generalized (bio)monitoring methods are lacking for assessing exposure to bisphenols.

## GRAPHICAL ABSTRACT

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## ABSTRACT

Bisphenol A (BPA) is ubiquitous in humans and the environment. Its potential adverse effects through genomic and non-genomic pathways have fostered BPA replacement by bisphenol analogs that, unfortunately, exert similar adverse effects. Many of these analogs, as well as their derivatives, have already found in humans and the environment and major concerns have arisen over their low dose- and mixture-related effects. This review aims to discuss the characteristics of the main analytical methods reported so far for the determination of mixtures of bisphenol analogs and/or derivatives in human and environmental exposure sources and biological fluids. Approaches followed for removal of background contamination, sample preparation and separation and detection of mixtures of bisphenols and derivatives are critically discussed. Sample treatment is matrix-dependent and common steps include analyte isolation, removal of interferences, evaporation of the extracts and solvent reconstitution. Separation and quantification has been almost exclusively carried out by liquid chromatography tandem mass spectrometry (LC-MS/MS) or gas chromatography mass spectrometry (GC–MS), in the last case prior derivatization, but LC-fluorescence detection has also found some applications. Main characteristics, advantages and drawbacks of these methods will be comparatively discussed. Although at an early stage, some approaches for the assessment of the risk to mixtures of bisphenols, mainly based on the combination of chemical target analysis and toxicity evaluation, have been already applied and they will be here presented. Current knowledge gaps hindering a reliable assessment of human and environmental risk to mixtures of bisphenols and derivatives will be outlined.



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**Contents**



## 1. Introduction

### 1.1. Bisphenols: uses and properties

Bisphenol A (BPA) is a high-production volume industrial chemical mainly used as a monomer in the production of polycarbonate plastics (~80%) and epoxy resins (~18%) [1–3]. Both of these polymers are widely used as food contact materials (viz. polycarbonate plastics in reusable food and drink containers, in tableware, and in water pipes, and epoxy resins as inner coatings of cans and lids of glass jars and bottles for food and beverages) [4–6].

No complete polymerization and/or polymer degradation account for leaching of BPA from consumer products to the surroundings. The serious concerns about the adverse effects of BPA on human health and aquatic life have led to industry to replace it with other bisphenols in some applications (Table 1) [7–9]. Because of the similarity in structure to BPA, the same or improved technical product properties as BPA can be obtained with the bisphenols included in Table 1. Unfortunately, toxicity profiles are also similar to BPA, with the disadvantage of being even less well-known within the scientific community [10].

Many other bisphenol-related compounds will undoubtedly contribute to the human and environmental exposure to bisphenols, namely chlorinated derivatives and bisphenol diglycidyl ethers. Chlorinated derivatives mainly result from the reaction of bisphenols with sodium hypochlorite, used as bleaching agent in paper factories and water disinfection (Table 1 shows as an example the chlorinated derivatives of BPA). Bisphenol diglycidyl ethers are the primary chemical building blocks for epoxy resins, epoxy-based lacquers or vinylic organosol (PVC) resins. The structures of bisphenol A and bisphenol F diglycidyl ethers (BADGE and BFDGE, respectively), as well as their hydrolytic and chlorinated derivatives, generated when the coating comes into contact with water and hydrochloric acid of the foodstuff during heat stabilization and storage, are also shown in Table 1 [11,12].

Properties of interest for the extraction, separation and detection of mixtures of bisphenols and derivatives (e.g. octanol–water partition coefficients and acid dissociation constants) are included in this table. Most of bisphenols are in the neutral form in samples and their mixtures encompass a wide range of polarity (eg. log $K_{ow}$ 1.254–6.564).

### 1.2. Levels for human and environmental exposure to bisphenols

Human and environmental exposure to bisphenols and their derivatives can be assessed either from estimated daily intakes [13–20] or biomonitoring [12,21,22]. Table 2 shows the concentrations found in the literature for bisphenols, chlorinated derivatives of BPA and diglycidyl ethers of BPA and BPF in human exposure sources, grouped according to the route of exposure (e.g. ingestion, dermal, inhalation), environmental compartments and biological samples. Only studies including more than one bisphenol or derivative, analyzed in at least 10 samples, have been considered for calculation of the results reported in Table 2 [12,14,15,23–61]. These results are expressed as arithmetic or geometric mean depending on the data reported in the respective studies. Also the whole range of concentrations found for the target compounds as well as their frequency of detection are shown in the table. When available, both free and total bisphenol concentrations have been included. These results are expected to give a rough picture of current human and environmental exposure to mixture of bisphenols.

Human exposure to bisphenols occurs primarily through ingestion of canned food and beverages [15,23–27,29–37,49–56,59,62–65] but also through skin absorption [14,66–68] and inhalation of dust [60] (Table 2). According to the results shown in Table 2, BPA continues being the bisphenol at the highest concentration and detection rate in foodstuffs, but