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Mini review

Recent trends in biomonitoring of bisphenol A, 4-t-octylphenol, and 4-nonylphenol

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ABSTRACT

Bisphenol A (BPA), 4-t-octylphenol (4-t-OP), and 4-nonylphenol (4-NP) are man-made alkylphenolic environmental contaminants possessing controversial endocrine disruption properties. Nowadays, an increased interest is raised for their accurate determination in biological media in order to estimate the exposure to these compounds and the associated health risk. The aim of this review is to present the available analytical methodologies for biomonitoring these three EDCs in human population. In non-occupational human exposure, they are detected in human matrices in trace level concentrations, commonly lower than 1 ng/mL. The use of mass spectrometry based methods is particularly emphasized due to their well known superiority over sensitivity, selectivity and precision, even in difficult matrices, such as blood plasma and serum. Recent and most applicable sample preparation techniques are thoroughly presented. The benefits of solid phase extraction (SPE) and expected developments are demonstrated. Recent results from exposure assessment and epidemiologic studies for BPA, 4-t-OP and 4-NP are summarized and future trends are discussed.

Contents

Abbreviations: BPA, bisphenol A; 4-t-OP, 4-t-octylphenol; 4-OP, 4-octylphenol (mixture of isomers); 4-NP, 4-nonylphenol (mixture of isomers); APs, alkyl phenols; APEOs, alkyl phenol ethoxylates; EDCs, endocrine disrupting compounds; LOD, limit of detection; LOQ, limit of quantification.

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1. Introduction

Bisphenol A (BPA), 4-t-octylphenol (4-t-OP), and 4-nonylphenol (4-NP) (mixture of isomers) are man-made alkyl phenols (APs), well known in the scientific world as xenoestrogen compounds (Fig. 1) (CERHR, 2008; Van Miller and Staples, 2005; Vazquez-Duhalt et al., 2005). BPA is a high production volume chemical mainly used in the industry as an important intermediate in the production of the following resins and polymers: polycarbonate, epoxy, polysulphone, polyacrylate, polyetherimide, unsaturated polyester and phenolic. It can be found in a wide variety of materials and products (e.g. bottles, coatings, pipes, dental sealants, food packaging, nail polishes and flame-retardant materials) that human population can easily come across on a daily basis (Ballesteros-Gomez et al., 2009; CERHR, 2008; Maragou et al., 2006, 2008a). Very recently, European Union (E.U.) banned the use of BPA in plastic infant feeding bottles, making a landmark move to safeguard infants and general population's health (Commission Directive 2011/8/EC, 2011). The other two APs, 4-t-OP and 4-NP were extensively used until recently in the E.U. and in the United States (U.S.) as intermediates in the production of phenolic resins and alkyl phenol ethoxylates (non-ionic detergents) (Van Miller and Staples, 2005; Vazquez-Duhalt et al., 2005). Alkyl phenol ethoxylates (APEOs) were used in industrial formulations (paper, leather, tannery, textile, oil industries and metal working fluids), antifoamers, detergents, dispersants, emulsifiers, paint ingredients, pesticide adjuvants and personal care products (Cox, 1996; DEFRA, 2008; Vazquez-Duhalt et al., 2005). Biodegradation of APEOs was proven to be an important source of 4-OP and 4-NP environmental contamination (David et al., 2009). Since 2000, 4-OP and 4-NP were included in the list of priority hazardous substances by Directive 2000/60/EC (Commission Directive 2000/60/EC, 2000). Since 2003, a reduction policy has been implemented in the E.U. for 4-NP (Commission Directive 2003/53/EC, 2003). Nowadays only a few countries (e.g. Asian countries) continue to use APEOs (David et al., 2009). Nevertheless, 4-t-OP and 4-NP are still widespread and detected world widely in environmental media, such as wastewaters, potable water, rivers and biota (David et al., 2009; Hawker et al., 2011; Gatidou et al., 2010; Stasinakis et al., 2008).

As xenoestrogen compounds, BPA, 4-t-OP and 4-NP present multiple modes of endocrine disruption activity; with the most emphasized being the binding to the estrogen receptors (estrogen receptors α and β) (Mueller and Korach, 2001) and acting competitively towards natural hormones (e.g. 17β-estradiol). Although the affinity of these APs towards the receptors are much weaker (weak estrogen activity) than the affinity naturally induced from the natural hormones of a living organism (CERHR, 2008; Sun et al., 2008; Van Miller and Staples, 2005; Vazquez-Duhalt et al., 2005), reproductive and developmental toxicity studies have shown effects to aquatic organisms and animals (Diamanti-Kandarakis et al., 2009; Krishnan et al., 2010; Staples et al., 2004; Van Miller and Staples, 2005; Vazquez-Duhalt et al., 2005). In the case of 4-NP, that occurs as a mixture of many isomeric compounds, it was clearly pointed out that estrogen activity may differ between isomers and was directly related to the form of the obtained alkyl chain structure (isomer-specific activity) (Reinscheid, 2009). Due to the large number of 4-NP isomers (293 isomers in total), research was focused on their separation, tandem mass detection and toxicity evaluation (Kammann et al., 2009; Lalah et al., 2007; Moeder et al., 2006; Preuss et al., 2008; Zenkevich et al., 2009). As presented in Moeder et al. (2006), tandem mass detection is important since the possibility to identify an isomer individually can be attempted only by its reported fragmentation pattern.

The exact endocrine disruption properties of BPA are controversial on human population, because, firstly and foremost, conflicting data can be found across exposure assessment studies and secondly, correlating findings on animals with potential effects on humans contains a degree of uncertainty (Vandenberg et al., 2010a,b). As far as 4-t-OP and 4-NP are concerned, a limited number of human toxicity studies have been carried out (Section 4.2), a fact that highlights the urgent need to investigate the toxicity and biotransformation pathways of these compounds in the human body. Therefore, biomonitoring of 4-t-OP and 4-NP in human fluids and tissues is deemed necessary in order to assist in elucidation of potential correlations between exposure and adverse health effects.

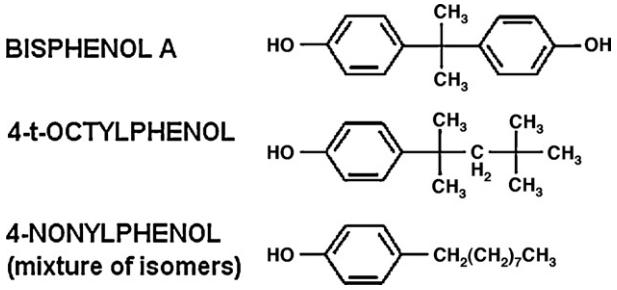

Fig. 1. Molecular structures of bisphenol A (BPA), 4-t-octylphenol (4-t-OP) and 4-nonylphenol (4-NP).

2. Biotransformation-biomarkers

When the three APs enter the blood circulation of the human body, biotransformation follows. At this point, the compounds are subject to glucuronidation and sulfation, mainly localized in the liver. Since they are converted in large extent into glucuronides and sulfates, their potential estrogenicity is deactivated. Then, the conjugates are rapidly cleared away from blood through the kidneys and end up in urine for excretion (Shangari et al., 2005). Due to biotransformation and rapid clearance, only low levels (trace levels) of the analytes are likely to be detected in blood after a specified time-period has elapsed from exposure. For instance, it was reported that BPA and 4-NP obtain approximately an elimination half-life in the human body of less than 6 (Völkel et al., 2002) and 3 h (Müller et al., 1998), respectively.

Therefore, biomonitoring should be performed through highly sensitive analytical methods and exposure assessment should be based, apart from the free species of the compounds, on the glucuronidated or/and sulfated conjugates. Glucuronide and sulfate species are present in urine and blood and can be used as biomarkers of exposure. When free plus conjugated species are quantified, then total concentration of the APs is determined and a more appropriate and integrated exposure evaluation is performed. Treatment of biological samples with glucuronidase and/or sulfatase enzyme during sample preparation prior to instrumental analysis is very common in order to cleave conjugate species and assess total concentration (Inoue et al., 2003a; Ye et al., 2005).

Due to the complexity of the alkyl phenol's metabolic pathways, biomarkers of exposure are an area of systematic research. Ye et al. (2007) identified 4-(3′,6′-dimethyl-3′-heptyl) catechol (P363-NC) in human liver microsomes as a potential biomarker for the main metabolite of one 4-t-NP isomer, 4-(3′,6′-dimethyl-3′-heptyl)phenol (P363-NP). 2-(3′,4′-dihydroxyphenyl)-2-(4′-hydroxyphenyl)propane (3-OH-BPA) (Nakagawa and Suzuki, 2001) and BPA catechol (Ye et al., 2011) may serve in the near future as potential biomarkers of human exposure to BPA. Suzuki et al. (2004) reported the detection of 3-OH-BPA even in river waters.