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Review

Analysis, toxicity, occurrence and biodegradation of nonylphenol isomers: A review

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ABSTRACT

Over the last two decades, nonylphenols (NPs) have become to be known as a priority hazardous substance due primarily to its estrogenicity and ubiquitous occurrence in the environment. Nonylphenols are commonly treated as a single compound in the evaluation of their environmental occurrence, fate and transport, treatment or toxicity. However, technical nonylphenols (tNPs) are in fact a mixture of more than 100 isomers and congeners. Recent studies showed that some of these isomers behaved significantly differently in occurrence, estrogenicity and biodegradability. The most estrogenic isomer was about 2 to 4 times more active than tNP. Moreover, the half lives of the most recalcitrant isomers were about 3 to 4 times as long as those of readily-biodegradable isomers. Negligence of NP's isomer specificity may result in inaccurate assessment of its ecological and health effects. In this review, we summarized the recent publications on the analysis, occurrence, toxicity and biodegradation of NP at the isomer level and highlighted future research needs to improve our understanding of isomer-specificity of NP.

Contents

1. Introduction

Nonylphenols (NPs) are widely recognized environmental pollutants and one of the 13 priority hazardous substances listed in European Union (European Union, 2008). A high production volume chemical, NP is primarily used as the raw material for the production of nonylphenol polyethoxylates (NPEOs), the most widely used nonionic surfactants (Ying et al., 2002). Nonylphenol polyethoxylates are used as detergents, emulsifiers, wetting and dispersing agents, antistatic agents, demulsifiers and solubilisers in domestic, agricultural and industrial products (Soares et al., 2008; Ying et al., 2002). The production of technical nonylphenols (tNPs, CASRN: 84852-15-3) in the United States was about 100–500 million lbs (45–227 thousand metric tons) in 2006 (USEPA, 2006). The dominant source of NP in the environment is partial biodegradation of NPEOs rather than direct discharges (Giger et al., 2009; Soares et al., 2008). In the wastewater treatment plants (WWTPs), biodegradation shortened the ethoxylate chain of NPEOs and under anaerobic conditions, complete de-ethoxylation and formation of NP are known to occur. Short-chain NPEOs may also be oxidized to form nonylphenoxy ethoxy acetic acid and nonylphenoxy acetic acid.

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Further biodegradation of these compounds may also result in NP. More detailed pathways on the origin of NP may be found in a few earlier reviews (Giger et al., 2009; Soares et al., 2008; Ying et al., 2002).

Technical nonylphenols have a water solubility of 4.9 mg/L, *log* K_{ow} of 4.48, vapor pressure of 2.07×10^{-2} Pa (at 25 °C) and pK_a of 10.28 (Soares et al., 2008). Nonylphenols are well known as endocrine disrupting compounds (EDCs), as they may mimic 17β-estradiol, with a mean potency (relative to 17β-estradiol) of 0.023 in *in vivo* bioassays (Soares et al., 2008). Bechi et al. (2010) reported that NP was capable of affecting cytokine secretion in human placenta at environmental levels (0.022 ng/L to 220 ng/L).

Nonylphenols have been frequently detected in water, sediment, sludge and soil (Soares et al., 2008; Ying et al., 2002). According to a national reconnaissance conducted by the U.S. Geological Survey investigating 139 streams across 30 states in the United States during 1999 and 2000, the median and maximum concentrations of NP were 0.8 and 40 μg/L, respectively, with a detection frequency of 50.6% (Kolpin et al., 2002). In a recent study, NP was found in 55 out of 62 drinking water samples from 31 major cities across China with median and maximum concentrations of 27 and 558 ng/L, respectively, and in all 62 source water samples with median and maximum concentrations of 123 and 918 ng/L, respectively (Fan et al., 2013). After analyzing the samples from the U.S. EPA's 2001 National Sewage Sludge survey, Venkatesan and Halden concluded that the concentration of NP in sludge was 534 ± 192 mg/kg with 100% detection frequency (2013). The mean annul loading of NP to sewage sludge was 2066–5510 metric tons, of which 1033 to 3306 metric tons was introduced into the environment via land application of biosolids (Venkatesan and Halden, 2013). The U.S. EPA guideline on NP for ambient water quality stipulates limits of 6.6 μg/L and 1.7 μg/L in freshwater and saltwater, respectively (Soares et al., 2008). In European Union, the maximum limit of NP in the sludge for land use is set at 50 mg/kg (European Commission, 2002) and the limit in surface water is 0.3 μg/L (European Union, 2008).

Nonylphenols are commonly treated as a single compound in the evaluation of their environmental occurrence, fate and transport, treatment removal and toxicity (Jiang et al., 2012; Soares et al., 2008; Ying et al., 2002). However, technical nonylphenols are in fact a mixture of more than 100 isomers and congeners due to variations in the length and branching of side chains and substitution position on the benzene ring (Eganhouse et al., 2009; Ieda et al., 2005). About 90% of tNP is made up by 4-NP and theoretically there are 211 constitutional isomers in 4-NP. Moreover, if stereoisomerism is considered, this number increases to 550 (Guenther et al., 2006). An increasing number of studies show that NP isomers have different estrogenicity and biodegradability in the environment (Eganhouse et al., 2009; Gabriel et al., 2008; Kim et al., 2005b; Shan et al., 2011), highlighting the importance to consider isomer specificity in understanding the environmental fate and risks of NP. The purpose of this review is to synthesize, and discuss recent literature on the analysis, toxicity and biodegradation of NP isomers. The Juelich numbering is used to name NP isomers due to its simplicity. The prefix number 4- indicating the substitution at the *para* position of benzene ring is usually omitted (Guenther et al., 2006) and suffix letters a and b are used to denote diastereomers (Table 1).

2. Analysis of nonylphenol isomers

2.1. Separation and identification

Separation and identification of NP isomers from tNP and environmental matrices are challenging tasks. To date several high performance liquid chromatography (HPLC) and gas chromatography (GC) methods have been reported on the separation of NP isomers (Table 2). HPLC methods have been often used to fractionate tNP for further studies (Gundersen, 2001), for example, estrogenic activity assays (Kim et al., 2004, 2005b). Therefore, these HPLC methods are not discussed here. Although the NP isomers have phenolic hydroxyl group, derivatization is not necessary before GC analysis (ISO, 2009; Moeder et al., 2006a; Thiele et al., 2004; Wheeler et al., 1997). Eganhouse et al. (2009) reported that alkylation of NP isomers did not provide any advantage in GC separation. Mass spectrometer detector (MSD) is the most commonly used detector for identifying the structures of NP isomers (Horii et al., 2004; Lu and Gan, 2014a; Moeder et al., 2006a,b; Thiele et al., 2004; Wheeler et al., 1997). Fourier transform infrared (FTIR) has also been used to confirm the substitution at *para* position (Wheeler et al., 1997). Synthesized NP isomers with structures confirmed by ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy have been included to compare and validate the mass fragmentation and retention time of isomers separated from tNP (Boehme et al., 2010; Russ et al., 2005; Thiele et al., 2004; Uchiyama et al., 2008; Yu et al., 2008).

Using high resolution capillary GC columns may resolve around 20 peaks (Horii et al., 2004; ISO, 2009; Kim et al., 2005b; Thiele et al., 2004; Wheeler et al., 1997). For instance, using a 100 m Petrocol DH column, Wheeler et al. (1997) successfully observed 22 peaks from tNP. Based on the mass fragmentation patterns, the authors divided these isomers into 5 groups. Thiele et al. (2004) used the same column to analyze a different tNP sample. Interestingly, the number of resolved peaks, the elution sequence and mass spectra of each isomer were exactly the same as in Wheeler et al. (1997). According to Wheeler et al. (1997), group 1 isomers had highly characteristic mass spectra: a base peak of *m/z* 135 and no other major peaks. The base peak of *m/z* 135 indicated that these isomers have dimethyl substituents at the α position and a lack of other major peaks suggested that the β carbon was not quaternary. Group 2 isomers had a base peak of *m/z* 135 and a major fragment of *m/z* 191. This group of isomers had one methyl and one ethyl substituent at α position and also no substituent at β position. The structures of group 1 and group 2 isomers have been confirmed by later studies using a two dimensional GC (GC × GC) method (Eganhouse et al., 2009), a GC tandem mass spectrometry method (Moeder et al., 2006a) and synthetic NP isomers (Gabriel et al., 2008; Katase et al., 2008; Russ et al., 2005; Shioji et al., 2006; Thiele et al., 2004). Group 3 isomers had a base peak of *m/z* 149 and no major peaks of *m/z* 163, 177 or 191. Wheeler et al. (1997) suggested that the lack of *m/z* 191 indicated no ethyl substitution at the α position and they proposed α-methyl-β-methyl structures for these isomers. However, Thiele et al. (2004) analyzed a synthetic isomer with this structure, i.e., 4-(1,2,5-trimethylhexyl)phenol, and found that this structure would only produce base peak of *m/z* 121. Katase et al. synthesized $NP_{110a/b}$ and found that the mass spectra and retention time matched with these group 3 isomers (Katase et al., 2008; Makino et al., 2008). Thus, group 3 isomers have α-methyl, α-ethyl and β-methyl substituents. Group 4 isomers had a base peak of *m/z* 163 and a major peak of *m/z* 121. Wheeler et al. (1997) suggested an α-butyl configuration for the formation of *m/z* 163 and suggested α-methyl and β-ethyl structures. Thiele et al. (2004) reported that *m/z* 121 could not be explained by this structure. Katase et al. (2008) and Makino et al. (2008) synthesized $NP_{193a/b}$ and finally determined that the substituents were α-methyl, α-n-propyl, and β-methyl. Group 5 isomers had an intense peak of *m/z* 121 and major peaks of *m/z* 163 and *m/z* 177. Wheeler et al. (1997) proposed α-methyl and α-propyl structures. After analyzing synthetic isomers NP_{194}, NP_{143} and NP_{152}, Thiele et al. (2004) split this group into two sub-groups, group 5 isomers with α-methyl and α-n-propyl substituents and group 6 isomers with α-methyl and α-*iso*-propyl substituents. The group 6 isomers had lower abundance of *m/z* 163, indicating that the cleavage of the *iso*-propyl group was preferred over the butyl group in MS analysis. Therefore, well characterized synthetic NP isomers have been instrumental in the separation and identification of NP isomers and will continue to be essential in the analysis of additional NP isomers.

Co-elution is one of the most critical problems in the analysis NP isomers by GC–MS. For example, according to Gabriel et al. (2008), the method used by ISO and many others (Guruge et al., 2011; Horii et al., 2004, 2010; ISO, 2009) had the co-elution of NP_{112}/NP_{128}, NP_{119}/NP_{152}