Occurrence, estrogen-related bioeffects and fate of bisphenol A chemical degradation intermediates and impurities: A review

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ABSTRACT

In recent decades, increasing attention has been directed toward the effects of bisphenol A (BPA) as an environmental pollutant, primarily due to its demonstrated endocrine-disruptive effects. A growing body of evidence indicates that many BPA derivatives also exhibit endocrine activity and other adverse biological properties. A review of the published literature was performed to identify BPA degradation intermediates resulting from chemical degradation processes of BPA, as well as BPA's associated co-pollutants. Products of biological metabolism were not included in this study. Seventy-nine chemicals were identified. Of these chemicals, a subset - those containing two 6-membered aromatic rings connected by a central ring-linking carbon - was identified, and a further literature review was conducted to identify demonstrated biological effects associated with the chemicals in this subset. The objectives of this review were to assess the potential risks to human and environmental health associated with BPA derivatives, characterize our current understanding of BPA's degradation intermediates and co-pollutants, and aid in the identification of compounds of interest that have received insufficient scrutiny.

KEYWORDS

bisphenol A, endocrine disruptors, organic pollutants, photodegradation products, estrogenic activity, thyroid activity.

1. Introduction

The endocrine activity of Bisphenol A (BPA) has long been known (Dodds & Lawson, 1936) and has been examined by an extensive body of research (Mattison et al., 2014; Peretz et al., 2014). As the prevalence of BPA-based plastics and epoxies has increased in recent decades, so have concerns regarding human and environmental exposure, leading BPA to be regarded as a threat to human and environmental health.

BPA is introduced into the environment through numerous pathways, such as wastewater treatment plant effluents, industrial discharge and landfill leachate (Corrales et al., 2015). BPA is concentrated in wastewater-treatment biosolids, which are dispersed on agricultural land as a supplement or alternative to conventional fertilizers (Langdon et al., 2010). Environmental exposure to BPA is widespread in soil, groundwater, surface water, and sediments (Zhu and Zuo, 2013; Careghini et al., 2015).

In recent years, attention has been increasingly turned toward the intermediates of BPA degradation through biological, chemical and photochemical processes. BPA's metabolites, chemical degradation intermediates and co-pollutants have increasingly been investigated as potential endocrine disruptors, genotoxins and toxicants. A thorough reading of this research will facilitate a more holistic understanding of the risks associated with the use of BPA.

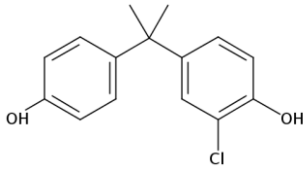
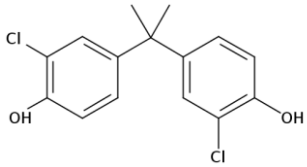
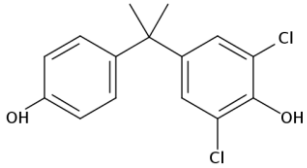
This work identifies the major BPA degradation intermediates resulting from chemical and photochemical processes described in the literature, as well as co-pollutants, such as impurities found in commercial BPA stock. It further reviews published works investigating the biological effects of these chemicals, including endocrine activity, cytotoxicity, genotoxicity and carcinogenicity. The current work deals with biological, especially estrogen-related, activity of BPA analogs and derivatives bearing two aromatic 6-membered rings connected by a single ring-linking carbon. Though not further

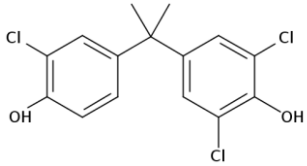
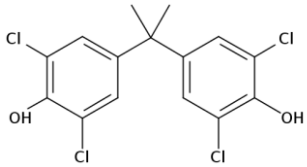
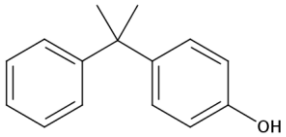
examined in this review, many other cleavage, addition and rearrangement products of BPA transformations exhibit endocrine activity and other biological effects. Products of environmental biological degradation and animal metabolism are outside the scope of this review, but are discussed in the cases of chemical species that result from both biological and abiotic processes. Table S1 summarizes BPA degradation products and intermediates generated through chemical pathways identified in the published literature, impurities, and co-pollutants analogous derivatives identified in several studies examining impurities in commercially available BPA. It also lists the published articles that identify these compounds as BPA derivatives.

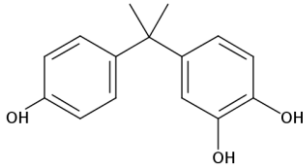
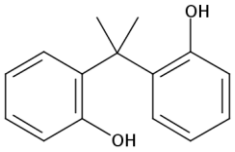
1.1 Transformation Pathways

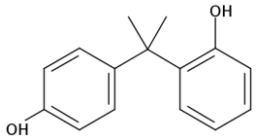
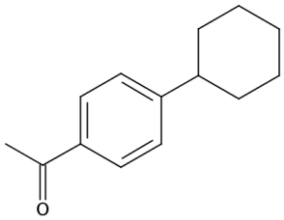
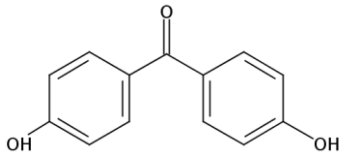
Predominant abiotic pathways for BPA degradation include photochemical and other chemical processes. The greater share of the published research focuses on methods for inducing degradation of BPA and other organic pollutants in the treatment of wastewater or drinking water. A number of studies also describe naturally occurring degradation pathways and inadvertent transformations occurring in drinking water treatment processes. In wastewater treatment, provisions for the induced degradation of organic pollutants are desirable, as a means of eliminating harmful chemicals before they are released into the environment. While the objective of any method for the treatment of organic pollutants should be complete mineralization or transformation into harmless organic species, stable intermediates may form. Recent years have seen an increased awareness of degradation intermediates as secondary pollutants. Traditionally, metrics of success have focused on the disappearance of primary pollutants. As a result, preventing or limiting the formation of organic intermediates, which may be more harmful than primary pollutants, has received relatively limited attention.

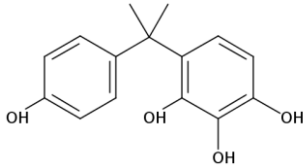
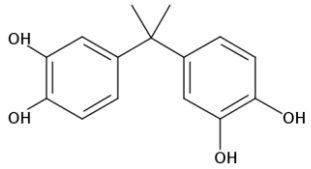
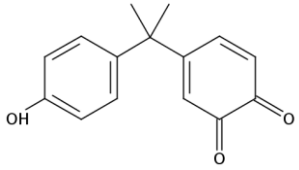
Table 1. BPA degradation intermediate products, impurities, and analogous derivatives identified in the literature, including the studies that have identified them and the experimental conditions. Structure images were taken from the SciFinder database.

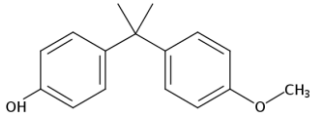
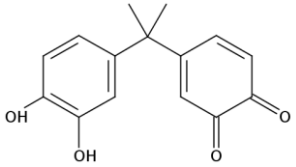
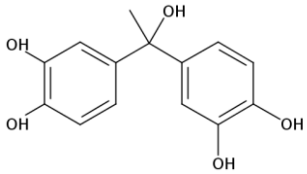
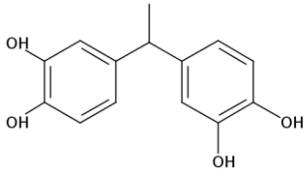
BPA derivative structure	**Name** **(abbreviated or common name)** **CAS number**	**Source discussing formation pathway or analytical determination**	**Experimental conditions of study**
	2-chloro-4,4'-isopropylidenediphenol (3-ClBPA) 74192-35-1	Fukazawa et al., 2001 Gallard et al., 2004 Lane et al., 2015 Liu et al., 2009	Analysis of effluents from paper recycling plants Reaction with HOCl Reactions with monochloramine, Cl_2 Photodegradation with Fe(III), fulvic acid, Cl^-
	4,4'-(1-methylethylidene)bis[2-chlorophenol] (3,3'-diClBPA) 79-98-1	Fukazawa et al., 2001 Gallard et al., 2004 Hu et al., 2002 Lane et al., 2015 Liu et al., 2009	Analysis of effluents from paper recycling plants Reaction with HOCl Reaction with NaClO Reactions with monochloramine, Cl_2 Photodegradation with Fe(III), fulvic acid, Cl^-
	2,6-dichloro-4-[1-(4-hydroxyphenyl)-1-methylethyl]phenol (3,5-diClBPA) 14151-65-6	Fukazawa et al., 2001 Gallard et al., 2004 Hu et al., 2002 Lane et al., 2015	Analysis of effluents from paper recycling plants Reaction with HOCl Reaction with NaClO Reactions with monochloramine, Cl_2

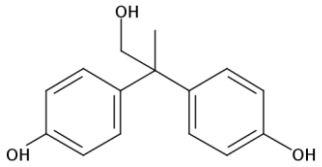
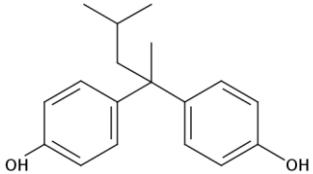
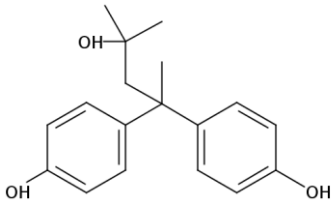
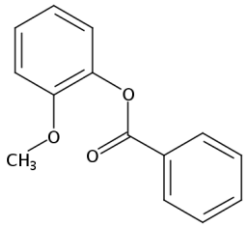
BPA derivative structure	Name (abbreviated or common name) CAS number	Source discussing formation pathway or analytical determination	Experimental conditions of study
	2,6-dichloro-4-[1-(3-chloro-4-hydroxyphenyl)-1-methylethyl]phenol (3,3',5-triClBPA) 40346-55-2	Fukazawa et al., 2001 Gallard et al., 2004 Hu et al., 2002 Lane et al., 2015	Analysis of effluents from paper recycling plants Reaction with HOCl Reaction with NaClO Reactions with monochloramine, Cl_2
	4,4'-(1-methylethylidene)bis[2,6-dichlorophenol] (TCBPA) 79-95-8	Fukazawa et al., 2001 Gallard et al., 2004 Hu et al., 2002 Lane et al., 2015	Analysis of effluents from paper recycling plants Reaction with HOCl Reaction with NaClO Reactions with monochloramine, Cl_2
	4-(1-methyl-1-phenylethyl) phenol (4-cumylphenol) 599-64-4	Terasaki et al., 2004	Impurities in industrial-grade BPA

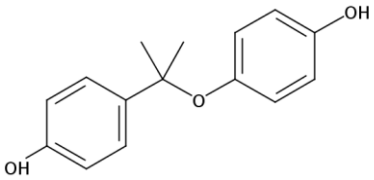
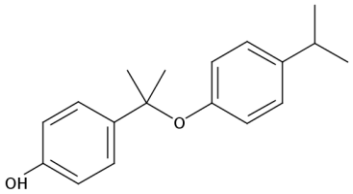
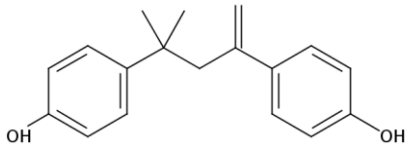
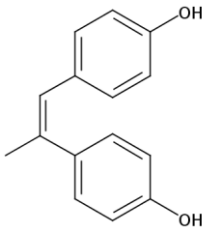
BPA derivative structure	Name (abbreviated or common name) CAS number	Source discussing formation pathway or analytical determination	Experimental conditions of study
	4-[1-(4-hydroxyphenyl)-1-methylethyl]-1,2-benzenediol (BPA catechol) 79371-66-7	da Silva et al., 2014*	Photodegradation with TiO catalyst
		Deborde et al., 2008	Ozonation reaction
		Ding et al., 2016	Photodegradation with $NaBiO_3$ catalyst
		Kanigaridou et al., 2017	Photodegradation with Cu-$BiVO_4$ catalyst
		Kondrakov et al., 2014	Photodegradation with TiO_2 catalyst
		Liu et al., 2010	Photodegradation with Fe(III), Cl^-, citric acid, NO_3^-
		Liu et al., 2011b*	Reaction in zero valent aluminum-acid system
		Mutou et al., 2006b	Photodegradation of BPA and chlorinated BPA derivs.
		Poerschmann et al., 2010	Oxidative Fenton reaction
		Sanchez-Polo et al., 2013	Photodegradation in H_2O_2 and Na_2CO_3 systems
		Torres et al., 2007*	Ultrasonic treatment; Fenton's reagent
		Torres et al., 2008	Ultrasonic treatment with O_2 saturation
		Torres-Palma, 2010	Photoassisted ultrasound/Fe^{2+}/TiO_2 process
		Zhan et al., 2006	Photodegradation with fulvic acid
		*Location of additional OH indeterminate)	
	2,2'-(1-methylethylidene) bisphenol 7559-72-0	Terasaki et al., 2004	Impurities in industrial-grade BPA

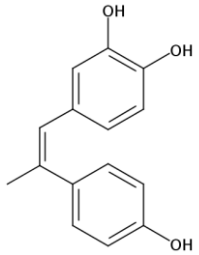
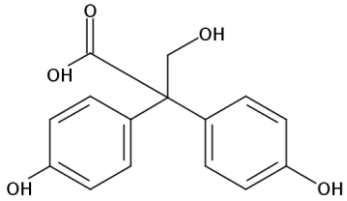
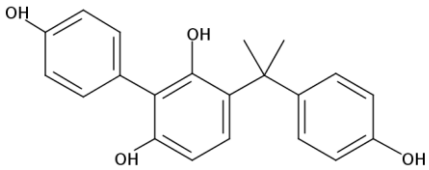
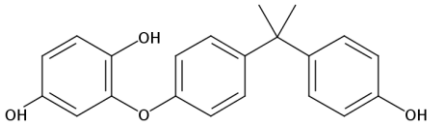
BPA derivative structure	Name (abbreviated or common name) CAS number	Source discussing formation pathway or analytical determination	Experimental conditions of study
	2-[1-(4-hydroxyphenyl)-1-methylethyl]phenol (*o*,*p*-bisphenol A) 837-08-1	Godínez et al., 2011 Nowakowska et al., 1996 Terasaki et al., 2004	Impurities detected in BPA Impurities detected in BPA Impurities in industrial-grade BPA
	1-(4-cyclohexylphenyl)ethanone (4-cyclohexylacetophenone) 18594-05-3	Molkenthin et al., 2013 Rodriguez et al., 2010	Photo-Fenton-like reaction with Fe^{3+} catalyst Photo-Fenton reaction with Fe(II), H_2O_2
	bis(4-hydroxyphenyl)methanone (bis4-HPM) 611-99-4	Molkenthin et al., 2013 Rodriguez et al., 2010	Photo-Fenton-like reaction with Fe^{3+} catalyst Photo-Fenton reaction with Fe(II), H_2O_2

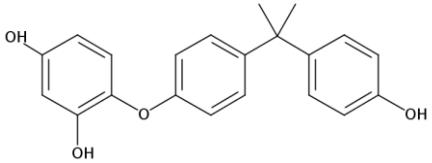
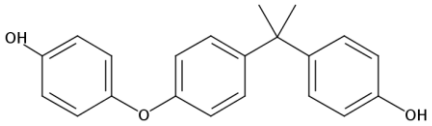
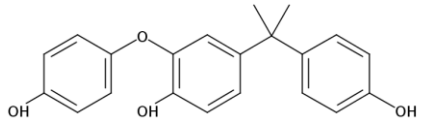
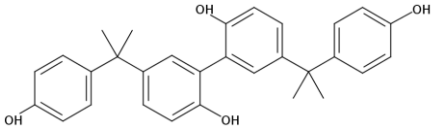
BPA derivative structure	Name (abbreviated or common name) CAS number	Source discussing formation pathway or analytical determination	Experimental conditions of study
	4-[1-(4-hydroxyphenyl)-1-methylethyl]-1,2,3-benzenetriol (2,3-OHBPA) 134954-771	da Silva et al., 2014* Torres et al., 2007* Torres et al., 2008* Torres-Palma, 2010 *Location of additional OHs indeterminate	Photodegradation with TiO catalyst Ultrasonic treatment; Fenton's reagent Ultrasonic treatment with O_2 saturation Photoassisted ultrasound/Fe^{2+}/TiO_2 process
	4,4'-(1-methylethylidene)bis[1,2-benzenediol] (BPA dicatechol) 18811-78-4	da Silva et al., 2014* Kondrakov et al., 2014 Poerschmann et al., 2010 Torres et al., 2007* Torres et al., 2008* Torres-Palma, 2010 *Location of additional OHs indeterminate	Photodegradation with TiO catalyst Photodegradation with TiO_2 catalyst Oxidative Fenton reaction Ultrasonic treatment; Fenton's reagent Ultrasonic treatment with O_2 saturation Photoassisted ultrasound/Fe^{2+}/TiO_2 process
	4-[1-(4-hydroxyphenyl)-1-methylethyl]-3,5-cyclohexadiene-1,2-dione (BPA 3,4-quinone) 163405-36-5	da Silva et al., 2014 Deborde et al., 2008 Kondrakov et al., 2014	Photodegradation with TiO catalyst Ozonation reaction Photodegradation with TiO_2 catalyst

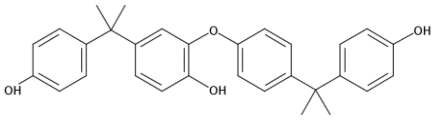
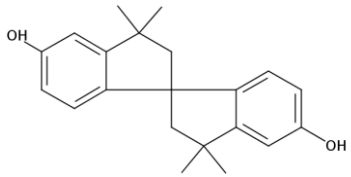
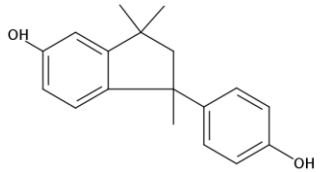
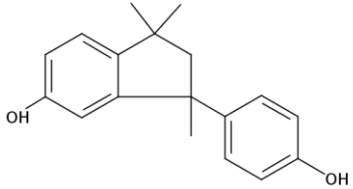
BPA derivative structure	Name (abbreviated or common name) CAS number	Source discussing formation pathway or analytical determination	Experimental conditions of study
	4-[1-(4-methoxyphenyl)-1-methylethyl]phenol (BPA monomethyl ether) 16530-58-8	Jia et al., 2012	Photodegradation with nano TiO_2 catalyst
	4-[1-(3,4-dihydroxyphenyl)-1-methylethyl]-3,5-Cyclohexadiene-1,2-dione 1422380-98-0	Kondrakov et al., 2014	Photodegradation with TiO_2 catalyst
	4,4'-(1-hydroxyethylidene)bis-1,2-benzenediol 1620838-56-3	Kanigaridou et al., 2017 Kondrakov et al., 2014	Photodegradation with Cu-$BiVO_4$ catalyst Photodegradation with TiO_2 catalyst
	4,4'-ethylidenebis-1,2-benzenediol 1620838-58-5	Kondrakov et al., 2014	Photodegradation with TiO_2 catalyst

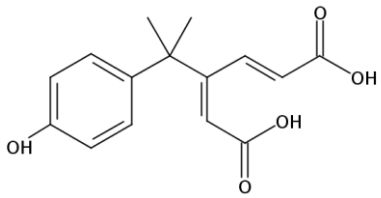
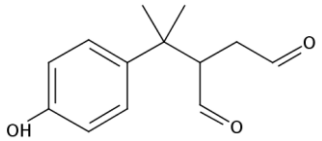
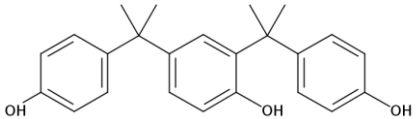
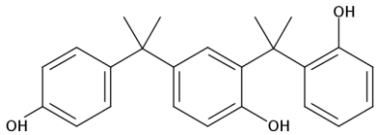
BPA derivative structure	Name (abbreviated or common name) CAS number	Source discussing formation pathway or analytical determination	Experimental conditions of study
	4-hydroxy-β-(4-hydroxyphenyl)-β-methylbenzeneethanol 142648-65-5	Poerschmann et al., 2010	Oxidative Fenton reaction
	4,4'-(1,3-Dimethylbutylidene)bisphenol 6807-17-6	Terasaki et al., 2004	Impurities in industrial-grade BPA
	4-hydroxy-γ-(4-hydroxyphenyl)-α,α,γ-trimethylbenzenepropanol 1334179-13-3	Poerschmann et al., 2010	Oxidative Fenton reaction
	2-methoxy-,1-benzoate phenol 531-37-3	Godínez et al., 2011	Impurities detected in BPA

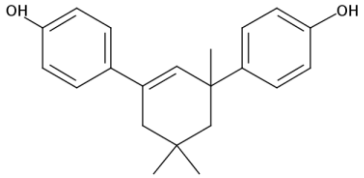
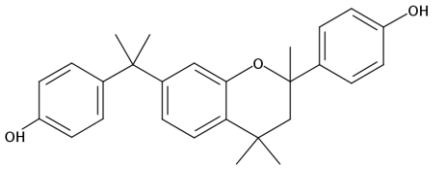
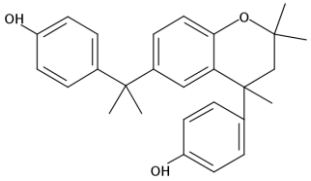
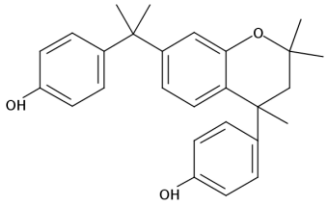
BPA derivative structure	Name (abbreviated or common name) CAS number	Source discussing formation pathway or analytical determination	Experimental conditions of study
	4-[1-(4-hydroxyphenoxy)-1-methylethyl]phenol 1151576-48-5	Lin et al., 2009 Poerschmann et al., 2010	Dark oxidative transformation in MnO_2 suspension Oxidative Fenton reaction
	4-[1-methyl-1-[4-(1-methylethyl)phenoxy]ethyl] phenol 1334179-10-0	Poerschmann et al., 2010	Oxidative Fenton reaction
	4,4'-(1,1-dimethyl-3-methylene-1,3-propanediyl)bisphenol 13464-24-9	Godínez et al., 2011	Impurities detected in BPA
	4,4'-(1-methyl-1,2-ethenediyl) bisphenol* 72108-22-6 *(double bond geometry undefined)	Poerschmann et al., 2010	Oxidative Fenton reaction

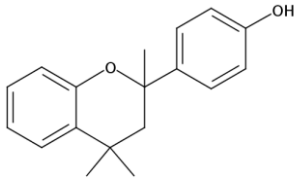
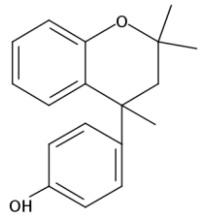
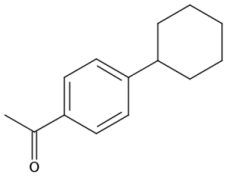
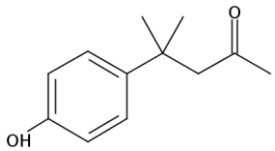
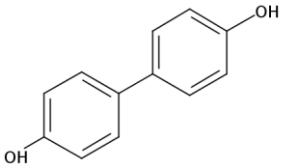
BPA derivative structure	Name (abbreviated or common name) CAS number	Source discussing formation pathway or analytical determination	Experimental conditions of study
	4-[2-(4-hydroxyphenyl)-1-propen-1-yl]-1,2-benzenediol 1133460-56-6	Poerschmann et al., 2010	Oxidative Fenton reaction
	4-hydroxy-α-(hydroxymethyl)-α-(4-hydroxyphenyl) benzeneacetic acid 1334179-11-1	Poerschmann et al., 2010	Oxidative Fenton reaction
	3-[1-(4-hydroxyphenyl)-1-methylethyl]-[1,1'-biphenyl]-2,4',6-triol 1334179-14-4	Poerschmann et al., 2010	Oxidative Fenton reaction
	2-[4-[1-(4-hydroxyphenyl)-1-methylethyl]phenoxy]-1,4-benzenediol 1334179-15-5	Poerschmann et al., 2010	Oxidative Fenton reaction

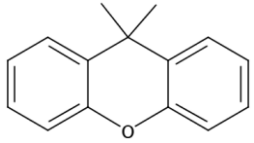
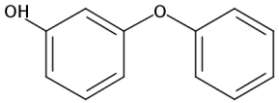
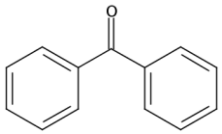
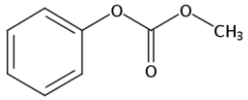
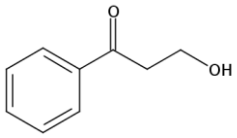
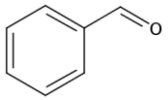
BPA derivative structure	Name (abbreviated or common name) CAS number	Source discussing formation pathway or analytical determination	Experimental conditions of study
	4-[4-[1-(4-hydroxyphenyl)-1-methylethyl]phenoxy]-1,3-benzenediol 1334179-16-6	Poerschmann et al., 2010	Oxidative Fenton reaction
	4-[1-[4-(4-hydroxyphenoxy) phenyl]-1-methylethyl]phenol 1151576-40-7	Lin et al., 2009 Poerschmann et al., 2010	Dark oxidative transformation in MnO_2 suspension Oxidative Fenton reaction
	2-(4-hydroxyphenoxy)-4-[1-(4-hydroxyphenyl)-1-methylethyl]phenol 1151576-43-0	Lin et al., 2009	Dark oxidative transformation in MnO_2 suspension
	5,5'-bis[1-(4-hydroxyphenyl)-1-methylethyl]-[1,1'-biphenyl]-2,2'-diol 134296-36-9	Lin et al., 2009 Poerschmann et al., 2010	Dark oxidative transformation in MnO_2 suspension Oxidative Fenton reaction

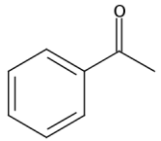
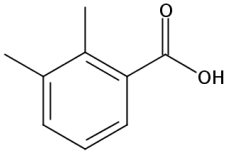
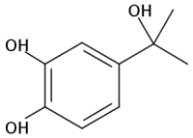
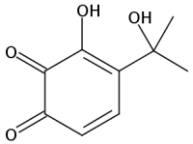
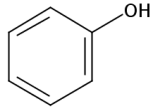
BPA derivative structure	Name (abbreviated or common name) CAS number	Source discussing formation pathway or analytical determination	Experimental conditions of study
	4-[1-(4-hydroxyphenyl)-1-methylethyl]-2-[4-[1-(4-hydroxyphenyl)-1-methylethyl] phenoxy]-phenol 158178-46-2	Lin et al., 2009 Poerschmann et al., 2010	Dark oxidative transformation in MnO_2 suspension Oxidative Fenton reaction
	2,2',3,3'-Tetrahydro-3,3,3',3'-tetramethyl-1,1'-spirobi[1-indene]-5,5'-diol 65192-06-5	Godínez et al., 2011	Impurities detected in BPA
	2,3-dihydro-1-(4-hydroxyphenyl)-1,3,3-trimethyl-1*H*-inden-5-ol 109252-41-7	Terasaki et al., 2004	Impurities in industrial-grade BPA
	2,3-dihydro-3-(4-hydroxyphenyl)-1,1,3-trimethyl-1*H*-inden-5-ol 10527-11-4	Terasaki et al., 2004	Impurities in industrial-grade BPA

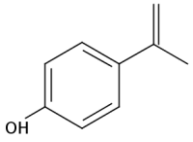
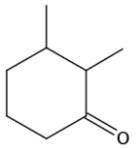
BPA derivative structure	Name (abbreviated or common name) CAS number	Source discussing formation pathway or analytical determination	Experimental conditions of study
	3-[1-(4-hydroxyphenyl)-1-methylethyl]-2,4-hexadienedioic acid 1334179-12-2	Deborde et al., 2008 Molkenthin et al., 2013 Poerschmann et al., 2010	Ozonation reaction Photo-Fenton-like reaction with Fe^{3+} catalyst Oxidative Fenton reaction
	2-[1-(4-hydroxyphenyl)-1-methylethyl]butanedial 1394897-50-7	Tay et al., 2012	Ozonation reaction
	2,4-bis[1-(4-hydroxyphenyl)-1-methylethyl]phenol 2300-15-4	Godínez et al., 2011 Nowakowska et al., 1996 Poerschmann et al., 2010 Terasaki et al., 2004	Impurities detected in BPA Impurities detected in BPA Oxidative Fenton reaction Impurities in industrial-grade BPA
	2-[1-(2-hydroxyphenyl)-1-methylethyl]-4-[1-(4-hydroxyphenyl)-1-methylethyl] phenol 745781-66-2	Terasaki et al., 2004	Impurities in industrial-grade BPA

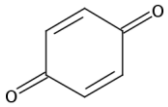
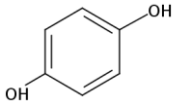
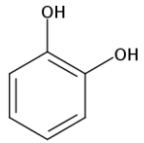
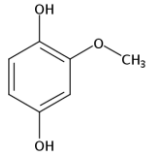
BPA derivative structure	Name (abbreviated or common name) CAS number	Source discussing formation pathway or analytical determination	Experimental conditions of study
	4,4'-(3,5,5-trimethyl-1-cyclohexene-1,3-diyl)bisphenol 745781-67-3	Terasaki et al., 2004	Impurities in industrial-grade BPA
	4-[3,4-dihydro-7-[1-(4-hydroxyphenyl)-1-methylethyl]-2,4,4-trimethyl-2H-1-benzopyran-2-yl]phenol 745781-68-4	Terasaki et al., 2004	Impurities in industrial-grade BPA
	4-[3,4-dihydro-6-[1-(4-hydroxyphenyl)-1-methylethyl]-2,2,4-trimethyl-2*H*-1-benzopyran-4-yl]-phenol 287110-79-6	Godínez et al., 2011	Impurities detected in BPA
	4-[3,4-dihydro-7-[1-(4-hydroxyphenyl)-1-methylethyl]-2,2,4-trimethyl-2*H*-1-benzopyran-4-yl]phenol 745781-69-5	Terasaki et al., 2004	Impurities in industrial-grade BPA

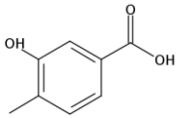
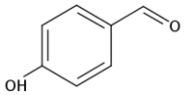
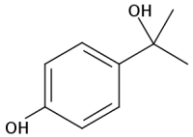
BPA derivative structure	Name (abbreviated or common name) CAS number	Source discussing formation pathway or analytical determination	Experimental conditions of study
	4-(3,4-dihydro-2,4,4-trimethyl-2H-1-benzopyran-2-yl)phenol 63661-69-8	Nowakowska et al., 1996 Terasaki et al., 2004	Impurities detected in BPA Impurities in industrial-grade BPA
	4-(3,4-dihydro-2,2,4-trimethyl-2H-1-benzopyran-4-yl)phenol 472-41-3	Nowakowska et al., 1996 Terasaki et al., 2004	Impurities detected in BPA Impurities in industrial-grade BPA
	1-(4-cyclohexylphenyl)ethanone 18594-05-3	Molkenthin et al., 2013 Rodriguez et al., 2010	Photo-Fenton-like reaction with Fe^{3+} catalyst Photo-Fenton reaction with Fe(II), H_2O_2
	4-(4-hydroxyphenyl)-4-methyl-2-pentanone 70205-18-4	Terasaki et al., 2004	Impurities in industrial-grade BPA
	4,4'-biphenyldiol 92-88-6	Lin et al., 2009	Dark oxidative transformation in MnO_2 suspension

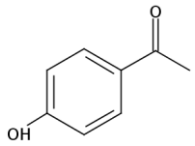
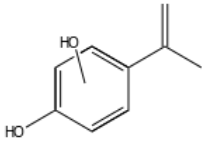
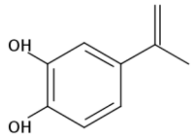
BPA derivative structure	Name (abbreviated or common name) CAS number	Source discussing formation pathway or analytical determination	Experimental conditions of study
	9,9-dimethyl-9*H*-xanthene 19814-75-6	Godínez et al., 2011 Nowakowska et al., 1996	Impurities detected in BPA Impurities detected in BPA
	3-phenoxyphenol 713-68-8	Sharma et al., 2016	Photodegradation in H_2O_2 and $Na_2S_2O_8$ systems
	diphenylmethanone 119-61-9	Sharma et al., 2016	Photodegradation in H_2O_2 and $Na_2S_2O_8$ systems
	methyl phenyl ester carbonic acid 13509-27-8	Godínez et al., 2011	Impurities detected in BPA
	3-hydroxy-1-phenyl-1-propanone 5650-41-9	Poerschmann et al., 2010	Oxidative Fenton reaction
	benzaldehyde 100-52-7	Olmez-Hanci et al., 2013 Rodriguez, et al., 2010	Thermally activated persulfate oxidation Photo-Fenton reaction with Fe(II), H_2O_2

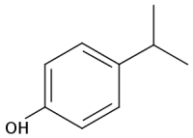
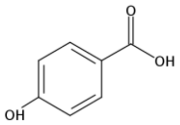
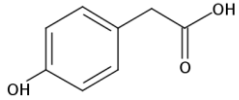
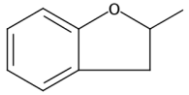
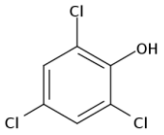
BPA derivative structure	Name (abbreviated or common name) CAS number	Source discussing formation pathway or analytical determination	Experimental conditions of study
	1-phenylethanone 98-86-2	Kaneco et al., 2004	Photodegradation with TiO_2 catalyst
	2,3-dimethylbenzoic acid 603-79-2	Olmez-Hanci et al., 2013	Thermally activated persulfate oxidation
	4-(1-hydroxy-1-methylethyl)-1, 2-benzenediol 1598425-53-6	da Silva et al., 2014 Kanigaridou et al., 2017 Kondrakov et al., 2014	Photodegradation with TiO catalyst Photodegradation with Cu-BiVO4 catalyst Photodegradation with TiO_2 catalyst
	3-hydroxy-4-(1-hydroxy-1-methylethyl)3,5-cyclohexadiene-1,2-dione 1598425-54-7	da Silva et al., 2014	Photodegradation with TiO catalyst
	phenol 108-95-2	Poerschmann et al., 2010 Rodriguez et al., 2010	Oxidative Fenton reaction Photo-Fenton reaction with Fe(II), H_2O_2

BPA derivative structure	Name (abbreviated or common name) CAS number	Source discussing formation pathway or analytical determination	Experimental conditions of study
	4-(1-methylethenyl)phenol 4286-23-1	Bechambi et al., 2016	Photodegradation with Ce-ZnO catalyst
		Chang, et al., 2013	Photodegradation with Bi/BiOI composite catalyst
		Ding et al., 2016	Photodegradation with $NaBiO_3$ catalyst
		Fukahori et al., 2003	Photodegradation with TiO_2-zeolite composite catalyst
		Godínez et al., 2011	Impurities detected in BPA
		Kanigaridou et al., 2017	Photodegradation with Cu-$BiVO_4$ catalyst
		Lin et al., 2009	Dark oxidative transformation in MnO_2 suspension
		Liu et al., 2011b	Reaction in zero valent aluminum-acid system
		Molkenthin et al., 2013	Photo-Fenton-like reaction with Fe^{3+} catalyst
		Poerschmann et al., 2010	Oxidative Fenton reaction
		Rodriguez et al., 2010	Photo-Fenton reaction with Fe(II), H_2O_2
		Sanchez-Polo et al., 2013	Photodegradation in H_2O_2 and Na_2CO_3 systems
		Sharma et al., 2016	Photodegradation in H_2O_2 and $Na_2S_2O_8$ systems
		Subagio et al., 2010	Photodegradation with nitrogen-doped TiO_2 catalyst
		Tay et al., 2012	Ozonation reaction
		Torres et al., 2007	Ultrasonic treatment; Fenton's reagent
		Torres et al., 2008	Ultrasonic treatment with O_2 saturation
		Zhan et al.; 2006	Photodegradation with fulvic acid
	2,3-dimethylcyclohexanone 13395-76-1	Sharma et al., 2016	Photodegradation in H_2O_2 and $Na_2S_2O_8$ systems

BPA derivative structure	Name (abbreviated or common name) CAS number	Source discussing formation pathway or analytical determination	Experimental conditions of study
	2,5-cyclohexadiene-1,4-dione	Ding et al., 2016	Photodegradation with $NaBiO_3$ catalyst
		Neamtu & Frimmel, 2006	Photodegradation of BPA
	106-51-4	Poerschmann et al., 2010	Oxidative Fenton reaction
	1,4-benzenediol	Ding et al., 2016	Photodegradation with $NaBiO_3$ catalyst
		Bechambi et al.; 2016	Photodegradation with Ce-ZnO catalyst
	(hydroquinone)	Fukahori et al., 2003	Photodegradation with TiO_2-zeolite composite catalyst
	123-31-9	Jia et al., 2012	Photodegradation with nano TiO_2 catalyst
		Lin et al., 2009	Dark oxidative transformation in MnO_2 suspension
		Liu et al., 2011b	Reaction in zero valent aluminum-acid system
		Lu et al., 2013	Photodegradation with $H_3PW_{12}O_{40}/TiO_2$ catalyst
		Molkenthin et al., 2013	Photo-Fenton-like reaction with Fe^{3+} catalyst
		Neamtu & Frimmel, 2006	Photodegradation of BPA
		Poerschmann et al., 2010	Oxidative Fenton reaction
		Tay et al., 2012	Ozonation reaction
		Torres et al., 2008	Ultrasonic treatment with O_2 saturation
		Zhan et al.; 2006	Photodegradation with fulvic acid
	1,2-benzenediol	Poerschmann et al., 2010	Oxidative Fenton reaction
	120-80-9		
	2-methoxy-1,4-benzenediol	Molkenthin et al., 2013	Photo-Fenton-like reaction with Fe^{3+} catalyst
	824-46-4		

BPA derivative structure	Name (abbreviated or common name) CAS number	Source discussing formation pathway or analytical determination	Experimental conditions of study
	3-hydroxy-4-methylbenzoic acid 586-30-1	Bechambi et al.; 2016 Olmez-Hanci et al., 2013 Sharma et al., 2016	Photodegradation with Ce-ZnO catalyst Thermally activated persulfate oxidation Photodegradation in H_2O_2 and $Na_2S_2O_8$ systems
	4-hydroxybenzaldehyde 123-08-0	Bechambi et al.; 2016 Fukahori et al., 2003 Subagio et al., 2010	Photodegradation with Ce-ZnO catalyst Photodegradation with TiO_2-zeolite composite catalyst Photodegradation with nitrogen-doped TiO_2 catalyst
	4-hydroxy-α,α-dimethylbenzenemethanol 2948-47-2	Deborde et al., 2008 Kanigaridou et al., 2017 Lin et al., 2009 Poerschmann et al., 2010 Subagio et al., 2010 Watanabe et al., 2003	Ozonation reaction Photodegradation with Cu-$BiVO_4$ catalyst Dark oxidative transformation in MnO_2 suspension Oxidative Fenton reaction Photodegradation with nitrogen-doped TiO_2 catalyst Photodegradation with TiO_2 catalyst

BPA derivative structure	Name (abbreviated or common name) CAS number	Source discussing formation pathway or analytical determination	Experimental conditions of study
	1-(4-hydroxyphenyl)ethanone 99-93-4	Ding et al., 2016	Photodegradation with $NaBiO_3$ catalyst
		Fukahori et al., 2003	Photodegradation with TiO_2-zeolite composite catalyst
		Kaneco et al., 2004	Photodegradation with TiO_2 catalyst
		Kanigaridou et al., 2017	Photodegradation with Cu-$BiVO_4$ catalyst
		Molkenthin et al., 2013	Photo-Fenton-like reaction with Fe^{3+} catalyst
		Poerschmann et al., 2010	Oxidative Fenton reaction
		Rodriguez et al., 2010	Photo-Fenton reaction with Fe(II), H_2O_2
		Sharma et al., 2016	Photodegradation in H_2O_2 and $Na_2S_2O_8$ systems
		Subagio et al., 2010	Photodegradation with nitrogen-doped TiO_2 catalyst
		Tay et al., 2012	Ozonation reaction
		Terasaki et al., 2004	Impurities in industrial-grade BPA
		Torres et al., 2007	Ultrasonic treatment; Fenton's reagent
		Torres et al., 2008	Ultrasonic treatment with O_2 saturation
	monohydroxylated 4-isopropenylphenol	Kanigaridou et al., 2017	Photodegradation with Cu-$BiVO_4$ catalyst
		Sanchez-Polo et al., 2013	Photodegradation in H_2O_2 and Na_2CO_3 systems
		Torres et al., 2007	Ultrasonic treatment; Fenton's reagent
		Torres et al., 2008	Ultrasonic treatment with O_2 saturation
	4-(1-methylethenyl)-1,2-benzenediol 186768-84-3	Molkenthin et al., 2013	Photo-Fenton-like reaction with Fe^{3+} catalyst
		Poerschmann et al., 2010	Oxidative Fenton reaction

BPA derivative structure	Name (abbreviated or common name) CAS number	Source discussing formation pathway or analytical determination	Experimental conditions of study
	4-(1-methylethyl)phenol 99-89-8	Liu et al., 2011b Lu et al., 2013 Olmez-Hanci et al., 2013 Sharma et al., 2016 Subagio et al., 2010 Watanabe et al., 2003	Reaction in zero valent aluminum-acid system Photodegradation with $H_3PW_{12}O_{40}/TiO_2$ catalyst Thermally activated persulfate oxidation Photodegradation in H_2O_2 and $Na_2S_2O_8$ systems Photodegradation with nitrogen-doped TiO_2 catalyst Photodegradation with TiO_2 catalyst
	4-hydroxybenzoic acid 99-96-7	Lu et al., 2013 Molkenthin et al., 2013 Poerschmann et al., 2010	Photodegradation with $H_3PW_{12}O_{40}/TiO_2$ catalyst Photo-Fenton-like reaction with Fe^{3+} catalyst Oxidative Fenton reaction
	4-hydroxybenzeneacetic acid 156-38-7	Poerschmann et al., 2010	Oxidative Fenton reaction
	2,3-dihydro-2-methylbenzofuran 1746-11-8	Kaneco et al., 2004	Photodegradation with TiO_2 catalyst
	2,4,6-trichlorophenol 88-06-2	Li et al., 2016	Reaction of BPA with NaClO

Advanced oxidation processes have been the main focus of recent research into the removal of organic pollutants in wastewater treatment. Recent works have studied the effects of photocatalysts such as bismuth vanadate ($BiVO_4$) (Kanigaridou et al, 2017), cerium-zinc oxide (Ce-ZnO) (Bechambi et al., 2016), BiOI (Chang et al., 2013) and sodium bismuthate ($NaBiO_3$) (Ding et al., 2016) on the degradation of organic pollutants. Catalytic effects of titanium dioxide (TiO_2) have been the focus of earlier and ongoing research into inorganic photocatalysts for the degradation of BPA (Fukahori et al., 2003; Watanabe et al., 2003; Torres-Palma, 2010; Jia et al., 2012; Kondrakov et al., 2014; da Silva et al., 2014). In addition to photocatalysts, Fenton's reagent may be used to oxidize organic contaminants in wastewater. Fenton and photo-Fenton reactions have been the focus of numerous BPA remediation studies (Molkenthin et al., 2013; Poerschmann et al., 2010; Rodriguez et al., 2010; Torres et al., 2007; Torres-Palma, 2010) and many organic intermediates have been identified in these works.

Real-world deployment of technologies for the treatment of organic pollutants varies substantially from place to place, and in many cases may be absent. Many of the methods for the photocatalytic treatment of organic pollutants discussed in the literature represent wastewater-treatment technologies that are primarily aspirational in nature and have not been applied in real wastewater treatment processes. Nevertheless, it can be assumed that the next generation of wastewater treatment technologies is represented in current and recent research. Therefore, a more comprehensive understanding of the implications of using these technologies in advance of their further development or deployment can lead to better-informed decisions regarding the environmental benefits and costs associated with their use.

In addition to processes applied to treat pollutants prior to their discharge into the environment, natural photochemical transformations in surface waters have been modeled experimentally (Calza et al., 2014; Zepp et al., 1985). Photochemical processes are believed to account for a substantial portion of BPA

degradation in the natural environment. Liu and colleagues (2009, 2010) investigated the solar photodegradation of BPA in surface waters, demonstrating the formation of chlorinated intermediates. Tercero Espinoza and colleages (2007) examined the degradation of BPA under simulated solar UV light. Several other studies have examined the effects of humic substances and dissolved organic matter as natural photosensitizers in the degradation of BPA and other phenolic compounds (Calza et al., 2014; Peng et al., 2006; Zhan et al., 2006). While substantial research has been conducted into the environmental degradation of BPA, studies identifying degradation intermediates are limited, and so our knowledge of these chemicals is incomplete.

In the treatment of drinking water, the objectives behind technologies currently in use are often sterilization and odor control, rather than detoxification of trace organic pollutants. Treatment with sodium hypochlorite (NaClO) is perhaps the most commonly deployed approach to meeting these objectives. NaClO reacts with BPA, which may be introduced to drinking water supplies through leaching from epoxy coatings in water pipes and water storage tanks (Liang et al., 2015). In wastepaper recycling, BPA - which occurs as a developer used in thermal printed papers (Shi, 2012) - comes in contact with NaClO, which is used as a bleaching agent. Products of reactions between NaClO and BPA have been found in effluents from paper recycling facilities (Fukazawa et al., 2001).

Reactions between BPA and NaClO proceed through several chlorinated BPA substitution intermediates to eventual cleavage products (Li et al., 2016; Tabata et al., 2004). The degree of BPA chlorination and degradation by NaClO is a function of both NaClO concentration and reaction time (Tabata et al., 2004). In real-world processes, the reaction sequence does not fully proceed to the cleavage step. Experimental evidence and water analysis have demonstrated that degradation of BPA by NaClO results in chlorinated bisphenol products and chlorinated phenolic cleavage products (Li et al., 2016).

1.2 BPA Impurities

Most risk assessments examining BPA's biological effects have been conducted using laboratory grade BPA, with 99+% purity. Industrial grade BPA more typically has a stated purity of 97-98% (Terasaki et al., 2004). Several analytical studies have examined industrial grade BPA, performing both quantitative and qualitative determination of the impurities (Godínez et al., 2011; Nowakowska et al., 1996; Terasaki et al., 2004). Limited data is available regarding the extent to which these impurities remain intact through polymerization and other chemical processes involved in producing BPA-based materials. It is probable that like BPA, some of these species may leach out of the finished materials, allowing for both human and environmental exposure.

1.3 Bio-effects of BPA Derivatives

BPA's estrogenic effects are the primary area of concern regarding its biological activity. As a result, research into the biological effects of BPA derivatives most frequently examines estrogenic activity, with several studies screening large numbers of chemicals for such activity using *in vitro* assays (Kitamura et al., 2005; Terasaki et al, 2005). Numerous *in vivo* studies have also examined smaller numbers of BPA derivatives, demonstrating estrogenic and other adverse effects in animals (Hasegawa et al., 2007; Kalasekar et al., 2015; Molins-Delgado et al., 2016; Nakazawa et al., 2009; Qiu et al., 2018). Due to structural similarities between BPA and bisphenol derivatives, many of the derivatives have been also found to be estrogen agonists.

A substantial share of the research into biological effects of BPA derivatives focuses on chlorinated bisphenols. Much of the interest in this area stems from the use of chlorinated and brominated bisphenols as flame retardants. Several of these chemicals have been found to exhibit biological activity not observed in BPA, such as thyroid hormonal activity (Butt & Stapleton, 2013; Fukazawa et

al., 2002; Letcher & Chu, 2010; Malkoske et al., 2016; Luo et al., 2016; Yamauchi & Ishihara, 2006).

Research conducted to-date has clearly demonstrated that the adverse biological effects associated with BPA are not limited to the effects of BPA itself. Rather, co-pollutants and BPA derivatives resulting from degradation processes pose substantial environmental and health risks. At this time, many chemicals structurally analogous to BPA have been subjected to a level of scrutiny insufficient to fully assess risk. Some chemicals remain altogether untested, and should be the focus of future research.

2. Chlorinated BPA Derivatives

2.1. Sources of Chlorinated BPA Derivatives

Chlorinated BPA derivatives have been shown to form in the presence of NaClO (Hu et al., 2002), and several studies include detailed kinetic analyses of NaClO-induced chlorination processes (Gallard et al., 2004; Lane, et al., 2015). Chlorination by NaClO is understood to proceed in a stepwise fashion in the following order: BPA → 2-chloro-4,4'-isopropylidenediphenol (3-ClBPA) → 4,4'-(1-methylethylidene)bis[2-chlorophenol] (3,3'-diClBPA) & 2,6-dichloro-4-[1-(4-hydroxyphenyl)-1-methylethyl]phenol (3,5-diClBPA) → 2,6-dichloro-4-[1-(3-chloro-4-hydroxyphenyl)-1-methylethyl]phenol (3,3',5-triClBPA) → 4,4'-(1-methylethylidene)bis[2,6-dichlorophenol] (TCBPA) (Li et al., 2016). This sequence is followed by a cleavage reaction with hypochlorite (ClO^-), resulting in chlorinated monoaromatic phenolic products. Experimental evidence (Tabata et al., 2004) and the prevalence of multiple chlorinated bisphenol compounds in treated drinking water (Fan et al., 2013) indicate that this pathway generally does not progress to completion outside of carefully controlled laboratory conditions, but rather results in residual concentrations of multiple chlorinated intermediates (Tabata et al., 2004). Chlorinated BPA derivatives found in sewage sludge (Song et al., 2014b) are likely evidence of chlorination occurring in municipal water treatment processes, in which NaClO is

used as a disinfectant.

Experimental evidence indicates that BPA also undergoes natural photo-chlorination reactions in the presence of sunlight in surface waters (Liu et al., 2009; Liu et al., 2010). Chlorinated BPA products, whether resulting from natural or induced processes, have been identified in the environment in surface waters (Yin et al., 2011) and sediment (Weiss et al., 2015).

In addition to being a product of BPA chemical transformation, TCBPA is also a widely used flame retardant. Introduction of TCBPA into the environment arises from both the manufacture or degradation of TCBPA treated products and the degradation of BPA. The current work includes discussion of TCBPA without further examination of the relative significance of the various environmental exposure pathways. The reader should bear in mind that the disproportionate attention paid to TCBPA in the literature relative to the other chlorinated BPA products results largely from the fact that TCBPA is a widely used industrial chemical. Given the wide range of demonstrated endocrine effects associated with TCBPA, the relatively limited body of research regarding the other chlorinated BPA derivatives likely represents an incomplete assessment of the biological and environmental hazards associated with chlorinated bisphenols, indicating a need for more research focused on this area.

3-ClBPA and 3,3'-diClBPA were shown to form in saline solutions in the presence of Fe(III) and fulvic acid in experiments designed to model reactions of BPA in sunlight in natural seawater (Liu et al., 2009). The rate of formation of chlorinated derivatives was substantially higher in the presence of both fulvic acid and Fe(III) than rates observed with either Fe(III) or fulvic acid alone, indicating a combined effect likely resulting from an Fe(III)-fulvic acid complex. Chlorination was also shown to occur in natural seawater. Chlorinated derivatives formed at concentrations approximately three orders

of magnitude below the BPA concentration, and concentrations tended to either decay or drop off after reaching a maximum, indicating that 3-ClBPA and 3,3'-diClBPA are able to undergo additional photo-transformation in seawater. A separate study (Liu et al., 2010) found that both nitrate and citric acid - used experimentally as a model for dissolved organic matter (DOM) - significantly suppressed the formation of both 3-ClBPA and 3,3'-diClBPA. However, the previous experiments in natural seawater suggest that these inhibitory effects may be minimal at environmental concentrations of nitrate and DOM.

2.2. Bioeffects of Chlorinated BPA Derivatives

2.2.1. Estrogenic Activity of Chlorinated BPA Derivatives

The endocrine-disruptive properties of chlorinated BPA products began receiving attention as early as 2002, with two *in vitro* studies. Fukazawa et al., (2002) examined estrogenic activity of the chlorinated BPA products with an agonist assay using the yeast two-hybrid system. 3-ClBPA, 3,3'-diClBPA, 3,5-diClBPA, 3,3',5-triClBPA and TCBPA were all found to exhibit estrogenic activity stronger than that of BPA. The most potent was 3,3'-diClBPA, with activity 38 times greater than that of BPA. It was also found that 3,3',5-triClBPA and TCBPA were resistant to biodegradation by an activated-sludge pathway, which is sometimes a key step in the decontamination of paper processing effluent, suggesting a potential for greater environmental exposure and persistence. In *in vitro* experiments with human breast carcinoma MCF7 cells, Kuruto-Niwa et al. (2002) demonstrated that 3-ClBPA and 3,3'-diClBPA had estrogenicities comparable to that of BPA at significantly lower concentrations. 3-ClBPA, 3,3'-diClBPA and 3,3',5-triClBPA were shown to strongly stimulate cancer cell proliferation, despite the enhanced cytotoxicity of chlorinated BPAs. These findings were supported by work using the MCF7 cell line, which found that 3-ClBPA stimulated cell proliferation at a rate comparable to that

of BPA, while 3,3',5-triClBPA and a mixture of 3,3'-diClBPA and 3,5-diClBPA both stimulated growth at a significantly higher rate than BPA (Liu et al., 2005). Additionally, it was found that a sample of BPA solution treated with 7 ppm NaClO stimulated greater cell proliferation than the untreated BPA solution, indicating that transformations occurring in water treatment processes may increase the endocrine activity of BPA.

Zebrafish are often used as a model species in the study of genetics and endocrine system behavior. Several studies have examined estrogenic effects of chlorinated BPA derivatives in zebrafish. Song and colleagues (2014a) examined estrogenic effects using a vitellogenin (VTG) assay. VTG is a protein used as a biomarker of estrogen exposure in vertebrates. While VTG levels were elevated in fish exposed to BPA (Letcher et al., 2005), no such change was observed with exposure to TCBPA. However, TCBPA exposure led to a significant increase in mortality over the control population in adult fish at concentrations at which BPA had no effect. Acute toxicity of TCBPA toward larvae and embryos was also much higher compared with that of BPA. A separate study using VTG analysis to measure estrogen agonist activity in Japanese medaka fish found that 3-ClBPA, and 3,3',5-triClBPA had lower estrogenicity than BPA, but that 3,3'-diClBPA was significantly more estrogen active than BPA, while TCBPA had no measurable estrogen agonist effect (Tabata et al., 2004).

More recently, a competitive-binding assay experiment demonstrated that at 1 μM, both BPA and TCBPA were effective competitors for estradiol (E2) binding to recombinant zebrafish G protein-coupled estrogen receptor 1, displacing 62% and 60% of E2, respectively (Fitzgerald et al., 2015). Both BPA and TCBPA were shown to disrupt oocyte maturation in zebrafish, measured by inhibition of germinal vesicle breakdown at concentrations as low as 5 nM.

Among other estrogenic effects observed in fish, TCBPA was shown in an *in vitro* experiment to be a

more potent inhibitor of E2 metabolism in the kidney and liver tissue of lake trout than BPA, reducing the formation of estrogen metabolites by approximately 80% at 100 μM (Jurgella et al., 2006). In considering effects within the liver, it should be noted that phenolic endocrine disrupting chemicals (EDCs) have been found to partition in the liver tissue of fish, such that biologically relevant concentrations at the site of the tissue may be significantly higher than those found in the organism as a whole or in the surrounding aquatic environment. Liu et al. (2011a) measured BPA at 106.7 ng/g dry weight in the liver of lake carp - approximately three times the concentrations occurring in gill and muscle tissue. The bioconcentration factor (ratio of BPA concentration in the fish to the surrounding aquatic concentration) was 29.

Kitamura et al., (2005) tested the endocrine activity of BPA and 19 related compounds, including bisphenols B, F, AF and S, tetrabrominated BPA, methylated bisphenols and several other bisphenol species. An MCF-7 estrogen luciferase reporter assay was used to test estrogenic activity, and showed that TCBPA was the most estrogenic of all compounds tested, showing significant agonist activity at 10^{-8} M. This finding is supported by other *in vitro* studies showing that TCBPA is more estrogenic than BPA (Fukazawa et al., 2002; Li et al., 2010; Ruan et al., 2015). However, contradictory evidence is found in the literature, suggesting that tetra-chlorination of BPA reduces estrogen agonist activity (Molina-Molina et al., 2013; Song et al., 2014a). Given the lack of consensus on this point, the effects of tetrachlorination on the estrogenic activity of BPA derivatives remains a subject of continued concern.

The estrogenic potential of TCBPA was examined *in vivo* using a uterotrophic assay with ovariectomized mice, and the estrogenic effect of both BPA and TCBPA was confirmed (Kitamura et al., 2005). In the *in vivo* experiment, TCBPA was found to exhibit somewhat lower estrogenic activity than BPA. The tendency of TCBPA to show limited effects on estrogen-driven cell and tissue growth

despite high estrogen receptor (ER) affinity could result from the heightened cytotoxicity observed in chlorinated bisphenols (Mutou et al., 2006b; Terasaki et al., 2011). Effects of cytotoxicity may account for some of the differences in estrogenicity measured using different methodologies.

Nuclear receptor binding has long been a favored metric for assessing endocrine activity of xenoestrogens. Due in part to limitations in the sensitivity of current bioanalytical techniques, measurable receptor binding tends to occur at higher concentrations than are biologically or environmentally relevant - a fact that contributes to the controversy surrounding the assessment of risk associated with EDCs such as BPA in real-world biological systems. Watson et al. (2014) and Vinas et al. (2013) focused on intercellular signaling mechanisms, rather than the more commonly studied nuclear transcriptional pathways, examining the effects of xenoestrogens on extracellular regulated kinases (ERK) at concentrations from 10^{-7} to 10^{-15} M. Across this concentration range, BPA, 3-ClBPA and 3,3'-diClBPA were found to enhance the effects of E2 on ERK activation in the presence of a natural E2 concentration, while 3,3',5-triClBPA deactivated ERK. Activation is associated with an increase in intercellular signaling, and deactivation results in suppression of natural signaling. This work provides strong evidence of low dose effects of BPA and its chlorinated derivatives at environmentally and biologically relevant concentrations, and may provide insight into the mechanisms behind non-monotonic dose-response curves associated with some EDCs.

Woeste and coworkers (2013) examined the ability of various bisphenols to interfere with the activity of the ion-translocating enzyme sarco/endoplasmis reticulum calcium ATPase (SERCA). Bisphenols have been shown to inhibit SERCA activity by binding to the enzyme. TCBPA was found to exhibit strong inhibitory activity, with an half-maximal inhibitory concentration (IC_{50}) 1/25 that of BPA. This demonstrates TCBPA's ability to interfere with Ca^{2+} homeostasis, resulting in elevated cytosolic Ca^{2+} levels and possibly bringing about apoptosis.

2.2.2. Thyroid Hormonal Activity of Chlorinated BPA Derivatives

Multiple studies have demonstrated that chlorinated bisphenols exhibit thyroid hormonal activity. 3,3',5-triClBPA and TCBPA have been shown to exhibit agonist activity with respect to 3,3',5-triiodothyronine (T_3) thyroid hormone, as well as antagonist activity through competition with T_3 for binding to thyroid hormone receptor α (TRα) (Terasaki et al., 2011). A GH3 assay used to test thyroid hormonal activity found that TCBPA induced thyroid hormone (TH)-dependent production of growth hormone in the range of 10^{-6} to 10^{-4} M, indicating agonist activity with respect to a T_3-dependent biological process. (Kitamura et al., 2005)

A combined *in vitro* and *in vivo* study has demonstrated the effects of chlorinated BPA derivatives in *xenopus laevis* frogs (Kudo & Yamouchi, 2005). Amphibians are useful to the study of TH disruption, as THs control amphibian metamorphoses. Chlorinated BPA compounds were shown to bind to *xenopus laevis* transthyretin (TTR) - a transport protein that carries the thyroid hormone thyroxine (T_4) in serum and cerebrospinal fluid - in competition with T_3. Binding potency was greatest for 3,3',5-triClBPA and least for 3-ClBPA. 3,3',5-triClBPA's binding affinity was 160 times greater than that of BPA, and just slightly less than that of T_3. In *xenopus laevis* tadpole experiments, exposure to 3,3',5-triClBPA was found to completely inhibit T_3-induced metamorphosis, indicating strong T_3 antagonist activity. In another study, TCBPA was shown to suppress tail shortening - an indicator of metamorphosis - in *rana rugosa* tadpoles at concentrations from 10^{-6} to 10^{-10} M (Goto et al., 2006). TCBPA also suppressed the T_3-induced apoptosis in tadpole tail muscle that is understood to be responsible for tail regression, and inhibited hindlimb elongation. An *in vitro study* developed a TH-responsive *xenopus laevis* cell line for use in a reporter gene assay (Sugiyama et al., 2005). Known and suspected thyroid-active compounds were tested for T_3 activity. 3,3',5-triClBPA exhibited T_3-antagonist activity at 0.01-1.0 μM. At concentrations from 0.01 to 10.0 μM, TCBPA exhibited T_3-like

agonist activity in cells incubated without T_3.

TCBPA was shown to inhibit thyroid hormone sulfotransferase activity in an *in vitro* assay using a 3,3'-diiodothyronine substrate in human liver cytosol, with an IC_{50} value of 340 nM (Butt & Stapleton, 2013). Thyroid hormone sulfonation - just one of multiple potential mechanisms for thyroid hormone disruption - aids the regulation of thyroid hormones by the formation of a biologically inactivated thyroid hormone. The sulfated hormone is deactivated by a subsequent deiodination. Inhibition of this process by TCBPA demonstrates TCBPA's ability to interfere with thyroid hormone regulation.

Competitive binding to TTR is a mechanism by which halogenated phenolic compounds appear to affect TH homeostasis. Compounds halogenated in the ortho positions with respect to hydroxyl groups on two phenolic rings, such as 3,3',5-triClBPA, have been shown to preferentially bind to TTR in amphibians (Yamauchi & Ishihara, 2006). In humans, preferential binding occurs when the halogens occupy both ortho positions on two rings, as is the case in TCBPA (Kudo & Yamauchi, 2005; Kudo et al., 2006).

Electrospray ionization mass spectroscopy (ESI-MS) was used to show that TCBPA binds to human and bovine serum albumin (Luo, et al., 2016). Among other functions, serum albumin functions as a transport protein for thyroid hormones, and may account for a portion of chlorinated-bisphenol transport in the human body.

2.2.3. Metabolic and Obesogenic Effects of Chlorinated BPA Derivatives

Endocrine disruptors, including chlorinated organic pollutants, have been shown to act as obesogens in animals (Cock and van de Bor, 2014; Lee et al., 2014). Several pathways involving peroxisome proliferator-activated receptors (PPARs) - a class of nuclear receptors that regulate the expression of

genes - have been implicated in obesogenic effects. While some of the possible mechanisms require ongoing exposure to stimulate sustained lipid mobilization, in the case of the PPARγ pathway, early limited-duration exposure to EDCs has been shown to cause effects later in life (Cock and van de Bor, 2014). An *in vivo* study demonstrated that TCBPA is readily absorbed during early stages of zebrafish larval development, and stimulates late-onset lipid accumulation in zebrafish exposed to concentrations of 100 nM early in development (Riu et al., 2014). TCBPA was shown to activate zebrafish PPARγ, offering a possible mechanistic explanation for the *in vivo* results.

Another zebrafish study determined that exposure of larvae to 1 nM TCBPA induced faster yolk absorption (Kalasekar et al., 2015). While this effect was not definitively attributable to PPARγ activation, it provides evidence of an increase in metabolic activity early in life, a factor associated with obesogenic effects. In addition to the *in vivo* evidence of metabolic effects, TCBPA was shown to induce adipogenesis in 3T3-Li cells in an i*n-vitro* experiment, demonstrating that TCBPA is a ligand and agonist for PPARγ in human cells (Riu et al., 2011).

Activation of PPARγ may have additional developmental implications beyond obesogenic effects. A rodent study (Wan Ibrahim et al., 2013) demonstrated that prenatal exposure to PPARγ-activating EDCs affects gene expression in neonatal brain tissue. Further investigation into developmental effects of chlorinated BPA derivatives by this pathway is warranted.

2.2.4. Other Endocrine-Disruptive Effects of Chlorinated BPA Derivatives

Chlorinated bisphenols have been shown to interact with retinoid X receptor (RXR) in a two-hybrid yeast assay (Li et al., 2016). RXRs play a role in regulating a wide range of biological processes, including cell growth, differentiation, metabolism, morphogenesis and embryonic development (Li et al., 2016; Tanaka and De Luca, 2009). Chlorination of BPA by NaClO led to a significant increase in

RXRβ antagonist activity with increasing chlorination of BPA derivatives. A proposed mechanism for the degradation of BPA by NaClO proceeds stepwise from monochlorinated products up to TCBPA and eventual cleavage to form 2,4,6-trichlorophenol (TCP), with exposure time and initial ClO^- concentration determining the extent to which this pathway proceeds (Li et al., 2016). TCP was shown to be the most potent RXRβ antagonist. TCBPA's and TCP's RXRβ antagonist activities were 7.09 and 79.31 times that of BPA, respectively, indicating that more thorough treatment with NaClO may significantly increase RXRβ antagonist activity of BPA in water treatment contexts by producing more TCP (Li et al., 2016).

TCBPA has been shown to exhibit strong progesterone-receptor antagonist effects in a bio-assay using a yeast strain transfected with a human progesterone response element. Effects were observable at concentrations as low as 10^{-8} M (Li et al., 2010). TCBPA was also found to be a weak-to-moderate human pregnane X agonist in a HeLa reporter bioassay, showing a greater potency in its ability to activate transcription via human pregnane E receptor than BPA (Molina-Molina 2013).

Published reports indicate either that TCBPA is not androgenic or that it is weakly androgenic. Several investigations into androgenic activity have found no androgen agonist effects (Kitamura et al., 2005; Molina-Molina et al., 2013; Sun et al., 2006). There is some evidence that TCBPA exhibits androgen antagonist properties (Li et al., 2010; Sun et al., 2006), but this is contradicted by research that has concluded that no such properties are present (Kitamura et al., 2005; Molina-Molina et al., 2013). Overall, it appears that TCBPA is at least significantly less anti-androgenic than BPA, which has been shown to be a strong androgen antagonist (Kitamura et al., 2005; Sun et al., 2006).

2.3. Chlorinated BPA Derivatives in Humans

Mono, di and tri-chlorinated derivatives of BPA have been detected in human adipose tissue in women,

with dichloro-BPA (either 3,3'-diClBPA or 3,5-diClBPA) found in 80% of samples, constituting an average of 94.6% of total chlorinated BPA detected. The mean concentration of dichloro-BPA detected was 9.21 ng/g - nearly twice the mean concentration of BPA. (Fernandez et al., 2007). Similar results were obtained from an analysis of adipose tissue in children, in which dichloro-BPA was found in 99% of samples, and was the most abundant of the chlorinated derivatives, although in children its mean concentration was somewhat lower than in adult women (Olea et al., 2008). Drinking water analyses have shown that dichloro-BPA represents a low percentage of overall chlorinated BPA derivatives (Fan et al., 2013), though data in this area are limited. Given that drinking water is thought to be the major source of exposure to chlorinated BPAs (Migeot et al., 2013), the biological concentrations suggest that dichloro-BPA's tendency to partition in adipose tissue is greater than that of BPA.

The possibility of maternal transfer of BPA and its chlorinated derivatives to newborns was raised by research showing that these chemicals are present in human colostrum - the nutrient and antibody-rich milk produced around the time of childbirth. 3,5-diClBPA was found in 100% of colostrum samples taken from 21 women. Mean concentrations of 3,3'-diClBPA and 3,5-diClBPA were 1.87 and 1.56 ng/ml, respectively, and were comparable to that of BPA (Migeot et al., 2013). BPA, and mono, di and trichlorinated derivatives were also detected in human placenta tissue (Jimenez-Diaz et al., 2010). BPA and dichloro-BPA were found in concentrations from 5.7-22.2 ng/g and 12.7-58.8 ng/g, respectively. BPA was detected in 20.4% of samples, whereas the 3 chlorinated derivatives were each found in approximately 50% of samples. In light of the demonstrated increase in endocrine activity with chlorination, the prevalence and abundance of the chlorinated derivatives suggest that neonatal and postnatal exposure to these chemicals may pose a greater risk to health and development than that posed by BPA. Evidence of fetal or neonatal exposure is particularly concerning given the demonstrated effects of short-term early exposure on PPAR mediated processes.

More recently, embryonic exposure to BPA and chlorinated BPAs was examined. The first 8 weeks of pregnancy are a crucial period in the development of the nervous and circulatory systems and the heart, so exposure to toxins and mutagens during this period can cause significant developmental abnormalities. During the first 8 gestational weeks, the embryo is housed in the chorionic villi, which covers the decidual membrane. These tissues serve as the interface between the mother and embryo during this stage of gestation. Chen and colleagues (2016) determined BPA and its chlorinated derivatives in decidua and chorionic villi samples collected from terminated pregnancies. 3-ClBPA, dichloro-BPA (a mixture of 3,3'-diClBPA and 3,5-diClBPA), 3,3',5-triClBPA and TCBPA were all detected, with 3-ClBPA and dichloro-BPA found in 76% and 72% of samples, respectively. In decidua, mean concentrations of 3-ClBPA (0.46 ng/g dw) and dichloro-BPA (0.43 ng/g dw) were highest among the chlorinated derivatives, but were below that of BPA (1.30 ng/g dw). In chorionic villi samples, frequency of occurrence was comparable, and mean concentrations of BPA, 3-ClBPA and dichloro-BPA were found to be 11.86, 3.70 and 4.30 ng/g dw, respectively. On the basis of a statistical analysis of correlations between analyte concentrations in placenta and chorionic villi samples, the researchers concluded that maternal transfer efficiency is higher for 3-ClBPA and dichloro-BPA than for BPA. Binding to TTR may offer a mechanistic pathway for transfer and accumulation in the embryo.

Chlorinated BPA derivatives have also been detected in human urine. Mono, di and trichloro-BPA were determined at mean concentrations of 0.055, 0.048 and 0.047 ng/ml, significantly lower than the mean BPA concentration of 0.701 ng/ml (Liao and Kannan, 2012).

2.4. Effects of Further Photodegradation of Chlorinated Bisphenols

Mutou and colleagues (2008) UV-irradiated chlorinated derivatives of BPA to assess the effects of photo-transformation on the chemicals' potential to induce or inhibit apoptosis. When Jurkat human

lymphoma cells were exposed to UVB or UVC-irradiated solutions of 50 μM 3-ClBPA, 3,3'-diClBPA and 3,3',5-triClBPA, cell viability was significantly decreased, indicating increased cytotoxicity in relation to non-irradiated solutions. Further irradiation reduced cytotoxicity. Induction of apoptosis was determined by analysis of DNA fragmentation and chromatin condensation. Chromatin condensation is a process by which chromatin is consolidated into chromosomes, and occurs in the prophase stage of cell mitosis. When Jurkat cells were exposed to 50 μM irradiated solutions of 3,3'-diClBPA, UVB and UVC-irradiated solutions induced chromatin condensation, while a UVA-irradiated solution and the non-irradiated 3,3'-diClBPA control did not. The UVB-irradiated solution also induced DNA fragmentation. These results are indicators that the species irradiated with UVB and UVC generated products that induced apoptosis. A biphasic relationship was observed between radiation exposure and apoptosis indicators, with effects initially increasing, then decreasing with increasing irradiation. This was attributed to chemical changes with continued irradiation, including loss of chlorine from the phenolic ring. In a prior work, irradiation of 3-ClBPA and 3,3'-diClBPA with UVB was shown to induce dissociation of chlorine, bringing about conversion to 4,4'-(1-methylethylidene)bis[1,2-benzenediol] (BPA dicatechol) and 4-[1-(4-hydroxyphenyl)-1-methylethyl]-1,2-benzenediol (BPA catechol), and further irradiation resulted in eventual decomposition of these products (Mutou et al.; 2006b). The initial increase in cytotoxicity with irradiation can be explained in part by the production of the intermediate BPA catechol, which has been shown to be highly cytotoxic (Nakagawa and Suzuki, 2001). UVB irradiation of 3,3'-diClBPA was shown to decrease estrogen agonist activity in a yeast two-hybrid assay in proportion to the release of chlorine (Mutou et al., 2006a).

Modification of histone proteins has been associated with the initiation and promotion of cancer. Phosphorylation of H2AX, a component of the protein histone H2A, occurs after the formation of double-stranded breaks in DNA (Rogakou et al., 1998). A culture of human keratinocyte skin cells

448 treated with UVB-irradiated 3,3'-diClBPA showed evidence of phosphorylated H2AX, indicating
449 double-stranded DNA breaks (Ibuki et al., 2008). No such effect was observed in untreated cells or
450 cells treated with irradiated BPA. A dose-dependent relationship was observed between UVB
451 irradiation of 3,3'-diClBPA and foci of phosphorylated H2AX. The increase in 3,3'-diClBPA's capacity
452 for inducing DNA breaks was attributed to formation of BPA catechol.

453 **3. Quinones and Hydroxylated Derivatives of BPA**

454 *3.1. Sources of Quinones and Hydroxylated Derivatives of BPA*

455 Hydroxylated derivatives of BPA are common to a variety of degradation pathways, including
456 chemical (Deborde et al., 2008; Ding et al., 2016; Liu et al., 2011b; Tay et al., 2012), photochemical
457 (da Silva et al., 2014; Ding et al., 2016; Kanigaridou et al., 2017; Kondrakov et al., 2014; Liu et al.,
458 2010; Mutou et al., 2006b) and sonochemical processes (Torres et al., 2007; Torres-Palma, 2010). In
459 addition to being identified as a BPA photodegradation product, BPA catechol has been shown to form
460 from BPA through metabolic pathways in animal (Nakagawa & Suzuki, 2001) and human (Ye et al.,
461 2011) hepatocytes.

462 Quinone derivatives of BPA result from photochemical processes (da Silva et al., 2014; Kondrakov et
463 al., 2014;) and BPA ozonation pathways (Deborde et al., 2008.)

464 *3.2. Bioeffects of Quinones and Hydroxylated Derivatives of BPA*

465 BPA catechol exhibits cytotoxic properties (Mutou et al., 2006b), and in animal cells is tranformed to
466 4-[1-(4-hydroxyphenyl)-1-methylethyl]-3,5-cyclohexadiene-1,2-dione (BPA 3,4-quinone), a DNA-
467 reactive species that has been shown to form DNA adducts *in vitro* and *in vivo* (Atkinson & Roy,
468 1995a; Atkinson & Roy, 1995b; Edmonds et al., 2004; Qui et al., 2004). The conversion of BPA

catechol to BPA 3,4-quinone *in vivo* is a crucial step in a proposed mechanism for cancer initiation induced by BPA metabolism. Briefly, BPA metabolism results in the production of BPA catechol, which is converted to BPA 3,4-quinone by an oxidative process. The electrophilic BPA 3,4-quinone reacts with DNA to form depurinating adducts, Depurination of the adducts results in apurinic sites on the DNA. If not repaired, these altered segements of DNA could be replicated, resulting in gene mutations, possibly leading to cancer initiation (Cavalieri & Rogan, 2010). Analytical (Edmonds et al., 2004) and computational (Kolsek et al., 2012; Kolsek et al., 2013) evidence demonstrates the formation and depurination of DNA adducts by BPA 3,4-quinone, and computational analysis indicates that adduct formation may be mediated by preferential reaction between BPA 3,4-quinone and scavengers such as glutathione within the cell (Kolsek et al., 2013). While this pathway is generally understood to progress from metabolic transformation of BPA, the crucial roles of BPA catechol and BPA 3,4-quinone in the sequence also warrant consideration of exogenous sources of these chemicals, such as the photochemical transformation of BPA.

DNA damage brought about by BPA 3,4-quinone may also result from intracellular generation of reactive oxygen species (ROS). In *in vitro* experiments, BPA 3,4-quinone was able to convert xanthine dehydrogenase (XD) - an enzyme associated with the metabolism of purines - to xanthine oxidase (XO) in rat hepatocytes (Sakuma et al., 2010). Unlike XD, the XO form of the protein is responsible for the production of ROS. Exposure to BPA 3,4-quinone was shown to induce oxidative DNA damage, likely attributable to XO-generated ROS.

Nakagawa & Suzuki (2001) investigated the estrogenicity of BPA catechol and BPA in a competitive binding assay. BPA catechol and BPA were both found to competitively displace E2 bound to estrogen receptor α (ERα), though binding potency was 3 orders of magnitude lower than that of the synthetic estrogen diethylstilbestrol. With an IC_{50} value of $5x10^{-5}$ M, BPA catechol was found to be slightly less

potent than BPA. In an MCF-7 bioassay, BPA catechol was shown to increase cell growth slightly at concentrations of 10^{-7} to 10^{-6} M, at a rate lower than that of BPA, likely due in part to BPA catechol's greater cytotoxicity (Nakagawa & Suzuki, 2001). BPA catechol was also found to be less estrogenic than BPA in a MCF-7 estrogen luciferase reporter assay, with a half maximal effective concentration (EC_{50}) of $1.8x10^{-6}$ M (Kitamura et al., 2005).

Exposure to BPA has been shown to be a contributing factor in neurodevelopmental disorders, raising the likelihood that BPA and its metabolites cross the blood-brain barrier. Ishido et al. (2011) examined the effects of BPA catechol and BPA 3,4-quinone on hyperactivity in rats, having previously demonstrated that neonatal BPA exposure elicits such behavior (Ishido et al., 2004; Ishido et al., 2007). Unlike BPA, BPA catechol and BPA 3,4-quinone were found to have no significant effect on spontaneous motor activity. BPA was found in the brain tissues of rats treated with BPA three weeks subsequent to exposure (Ishido et al., 2011). BPA catechol and BPA 3,4-quinone were not found in the brain tissues of rats treated with these chemicals, indicating a shorter residual time or failure to cross the blood brain barrier.

Evidence of estrogen and androgen antagonist activity among the hydroxylated and quinone BPA derivatives is limited. In an E2 assay system with MCF-7 cells, BPA catechol did not exhibit significant anti-estrogenic activity. In an NIH3T3 bioassay, BPA catechol showed weak anti-androgenic activity, several times lower than that of BPA (Kitamura et al., 2005).

Several of the hydroxylated or quinone BPA derivatives have received little or no experimental scrutiny from the perspectives of endocrine activity or other biological effects. Kondrakov and colleagues (2014) speculated that BPA dicatechol, 4,4'-(1-hydroxyethylidene)bis-1,2-benzenediol and 4,4'-ethylidenebis-1,2-benzenediol are less estrogenic than BPA. This analysis was based on Kitamura

514 and colleagues' (2005) finding that hydroxyl substitution on the aromatic rings or propane bridge
515 reduces estrogenicity. However, this hypothesis remains untested. Given that 4-[1-(4-hydroxyphenyl)-
516 1-methylethyl]-1,2,3-benzenetriol (2,3-OHBPA), BPA dicatechol, 4,4'-(1-hydroxyethylidene)bis-1,2-
517 benzenediol and 4,4'-ethylidenebis-1,2-benzenediol have not been closely examined, and given the
518 structural similarities to BPA catechol, which has been shown to undergo metabolic transformation to
519 mutagenic or genotoxic species, experimental data regarding these chemicals is needed.

520 **4. Bis(4-hydroxyphenyl)methanone**

521 *4.1. Sources of Bis(4-hydroxyphenyl)methanone*

522 The benzophenone bis(4-hydroxyphenyl)methanone (bis4-HPM) has been identified as a photoproduct
523 of BPA (Molkenthin et al., 2013; Rodriguez et al., 2010). Benzophenones are widely used as UV filters
524 in personal care products and industrial goods, and are prevalent in surface waters (Gago-Ferrero et al.,
525 2015) and sewage effluent and sludge (Ruan et al., 2015). Bis4-HPM has also been identified as a
526 biological metabolite of bisphenol F in rat urine (Cabaton et al., 2009). As a result of its multiple
527 sources and widespread environmental prevalence, it has received considerable scrutiny as an
528 environmental pollutant and as an EDC that is potentially harmful to human health.

529 *4.2. Bio-effects of Bis(4-hydroxyphenyl)methanone*

530 In an MCF-7 bioassay, 1 μM bis4-HPM was shown to stimulate cancer cell proliferation at a level
531 comparable to that brought about by E2 at 10 nM. In the same study, transcriptional activity was
532 investigated using an Sp1-Luciferase assay. In the activation of the Sp1 reporter gene, 1 μM bis4-HPM
533 was as potent as 0.010 μM E2 (Kerdival et al., 2013).

534 In an examination of the biological activity of several bisphenols and their derivatives, bis4-HPM was

found to exhibit dose-dependent genotoxicity at 200 μM (Cabaton et al., 2009). Estrogenic effects similar to those of bisphenol F were observed, with EC_{50} concentrations of 4.00 μM and 1.16 μM for ERα and ERβ, respectively. No anti-androgenic effects were observed. Estrogenicity of bis4-HPM was also examined in separate work using a bioluminescence yeast estrogen screen assay, which found that it was weakly estrogenic, with an EC_{50} concentration approximately 20 times that of BPA, and 6 orders of magnitude higher than that of E2 (Ruan et al., 2015).

Bis4-HPM has been found to bind to transport proteins, potentially interfering with natural intercellular hormone transport (Hong et al., 2015). It was shown to bind to human sex hormone-binding globulin, the major transport protein in serum that binds estrogens and androgens, and plays a role in regulating their availability to cells. Its IC_{50} concentration was approximately 1/7 that of BPA. Woeste and colleagues (2013) found that it's SERCA inhibitory potency was similar to that of BPA, with the two chemicals exhibiting comparable IC_{50} concentrations.

In vivo research examining the biological effects of bis4-HPM is limited. A recent study investigating the ecotoxicity of UV filters found that it was acutely toxic to *vibrio fischeri* bacteria, with an EC_{50} concentration of 9.9 mg/L (Molins-Delgado et al., 2016). Given the widespread prevalence of the chemical in aquatic systems, further examination of effects on aquatic species is warranted.

5. Other Bisphenol A Derivatives

2-[1-(4-hydroxyphenyl)-1-methylethyl]phenol (*o,p*-bisphenol A) is an isomer of BPA with close structural similarity to BPA. It is a byproduct of BPA synthesis and a common impurity found in BPA (Godínez et al., 2011; Nowakowska et al., 1996; Terasaki et al., 2004). *O,p*-bisphenol A has been the subject of several quantitative structure-activity relationship (QSAR) studies (Coleman et al., 2003; Cui et al., 2006; Klopman and Chakravarti, 2003) and at least two biological studies. Bioassay experiments,

examining human estrogen receptor α (hERα) binding affinity, gene induction and MCF-7 human breast cancer cell proliferation (all relative to E2) found that *o,p*-bisphenol A is slightly less endocrine active than BPA by all three measures (Coleman et al., 2003). Terasaki and colleagues (2005) found through yeast two-hybrid assay analysis that its binding affinites for hERα and medaka fish ERα were higher than that of BPA by factors of 3.0 and 1.4, respectively. The same study found that 2,2'-(1-methylethylidene)bisphenol - another BPA isomer and BPA impurity (Terasaki et al., 2004) - exhibits relative binding affinites for hERα and medaka fish ERα slightly lower than those of BPA.

4-Cumylphenol (4-CP) is another close structural analog to BPA that has been detected as an impurity in industrial grade BPA (Terasaki et al., 2004). In the marine environment, it has been found in lobster eggs, larvae and muscle tissue (Zuo et al., 2015; Laufer et al., 2013) and prawn muscle tissue (Zuo & Zhu, 2014). Terasaki and colleagues (2005) found that its binding affinities toward hERα and medeka fish ERα exceed the activity of BPA by factors of 12 and 6.5, respectively.

Sanseverino and colleagues (2009) examined 4-CP's estrogenicity using bioluminescent yeast assays and found that its EC_{20} (concentration of 20% maximal effect) was 840 nM - nearly three orders of magnitude lower than that of BPA. In addition to estrogenic activity, another yeast-assay study demonstrated that 4-CP's retinoic acid receptor binding affinity is several times higher than that of BPA (Kamata et al., 2008). In addition to *in vitro* evidence, i*n vivo* studies have shown that short-term exposure of newborn rats to 4-CP can cause lasting developmental abnormalities including reduced ovary growth (Hasegawa et al., 2007) and the occurrence of renal cysts (Nakazawa et al., 2009).

Coleman and colleagues (2003) found that the BPA photoproduct 4-[1-(4-methoxyphenyl)-1-methylethyl]phenol (BPA monomethyl ether) was less endocrine active than BPA as measured by hERα binding affinity, gene induction and MCF-7 human breast cancer cell proliferation. QSAR

analysis indicated that the methoxy group contributed to a deactivating effect in regards to hERα binding affinity. In an *in vitro* assay, BPA monomethyl ether was shown to induce the formation of multipolar spindles in mitotic HeLa cells to a degree comparable to that of BPA (George et al., 2008). Multipolar spindles are a cell defect that leads to chromosomal instability in cell division, and are commonly found in tumor cell lines. This finding demonstrated that both BPA monomethyl ether and BPA may be capable of disrupting cell division.

4-hydroxy-β-(4-hydroxyphenyl)-β-methylbenzeneethanol has been identified as a degradation product of BPA via a Fenton reaction pathway (Poerschmann et al., 2010). Effects of bisphenol analogues on induction of pS2 protein (a measure of estrogen-controlled gene expression) and progesterone receptor (PgR) were examined in a bioassay study using MCF-7 cancer cells (Rivas et al., 2002). 4-hydroxy-β-(4-hydroxyphenyl)-β-methylbenzeneethanol was found to significantly increase PgR and pS2 levels. In the same study, using an MCF-7 cell proliferation assay, it was found to increase cell yield seven-fold at a concentration of 10 μM. Estrogenicity was confirmed using an MVLN (an MCF-7 derived cell line) luciferase induction assay, and a significant effect was seen at 10 μM. This is comparable to results observed in a separate study using an MCF-7 estrogen luciferase reporter assay (Kitamura et al., 2005). In the latter study, 4-hydroxy-β-(4-hydroxyphenyl)-β-methylbenzeneethanol was also found to be inactive as an anti-androgen. In addition to empirical data, estimates of environmental risk using the OECD (Q)SAR Application Toolbox software predicted that it is a strong estrogen binder, but is likely not significantly bioaccumulative, with a bioconcentration factor of 7.1 (Koleva and Georgieva, 2013).

6. Structure and Endocrine Activity

ER binding activity is highly dependent on chemical structure. ER binding depends on a favorable interaction between an estrogen or xenoestrogen and a receptor's binding pocket, which is larger in

volume than the typical bisphenol molecule, and is lined with nonpolar residues that interact favorably with nonpolar moieties. Binding requires a phenolic ring attached to nonpolar regions aligned with the central portions of the binding pocket, meaning that hydrophobic substituents on the ring-linking carbon in bisphenols tend to increase estrogenicity (Coleman et al, 2003; Molina-Molina et al., 2013).

Experimental data have shown that a 4-hydroxyl substituent on one of the phenolic rings is most effective at facilitating binding, but hydroxyl groups in the 2 or 3 position have also been shown to be effective (Kitamura et al., 2005). Comparisons between estrogen agonist activities of BPA and 4-CP offer an inconclusive assessment of the effects of a 4-hydroxyl group on the second phenolic ring. Paris and colleagues (2002) found that the second 4-hydroxyl group greatly increased ERα and ERβ binding. Contradictory data obtained by Terasaki and colleagues (2005) indicate that estrogenic activity is greater in the absence of the second 4-hydroxyl group.

The effect of halogenation on estrogenic activity is also uncertain. A comparative study of BPA, tetrabromo-BPA (TBBPA) and TCBPA showed that TCBPA has a significantly higher estrogen receptor binding affinity than BPA (Kitamura, et al., 2005). On the other hand, Riu et al., (2011) found that TCBPA had lower agonist activity than BPA toward ERα and estrogen receptor β (ERβ), while Rivas et al. (2001) found that TCBPA had lower estrogenic activity than BPA in an MCF-7 cell proliferation bioassay. While increased cytotoxicity in the halogenated species (Mutou et al., 2006b; Terasaki et al., 2011) may partially explain the inconsistencies in these results, nothing definitive can be said at this time regarding the effects of chlorination on estrogenicity. Less evidence is available regarding the effects of bromination. It has been shown that 3,5 bromination in TBBPA reduces binding affinity compared with that of BPA, and that binding affinity is lower than that of TCBPA. This may be due to steric hindrance from the larger bromine substituent (Kitamura et al., 2005).

Evidence of thyroid agonist activity among bisphenol A derivatives is limited, and is mostly seen only in halogenated species, such as TCBPA, 3,3',5-triClBPA and TBBPA. Species with halogen substituents in adjacent positions on either or both sides of a phenolic hydroxyl group tend to have greater thyroid activity. These species are structurally analogous to T_3 and T_4, each of which have a phenolic hydroxyl group adjacent to 1 or 2 iodine substituents, respectively (Fig. 1). Steric factors may play a role in determining how the identity of the halogen affects TH receptor binding. While some evidence shows that TBBPA is more thyroid active than TCBPA (Kitamura et al., 2005), other research has reached the opposite conclusion (Terasaki et al., 2011).

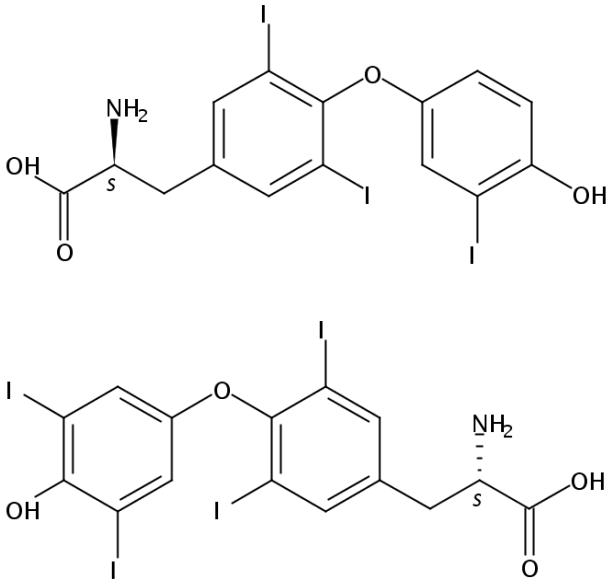


Figure 1. Thyroid hormones T_3 (3,3',5-triiodothyronine - top) and T_4 (thyroxine)

BPA has been shown to exhibit anti-androgenic activity (Kitamura et al., 2005; Paris, et al., 2002). Kitamura and colleagues' (2005) comparative study demonstrated that at least one 4-hydroxyl group is necessary for androgen inhibition to occur. Additional substituents in the adjacent 3 and 5 positions on phenolic rings reduce anti-androgenic activity (Sun et al., 2006; Kitamura et al., 2005). Evidence regarding anti-androgenic activity in this review is limited, and generally shows that most BPA

636 derivatives tend to be less anti-androgenic than BPA.

637 **7. Conclusions and future prospects**

638 Bisphenol A is a synthetic estrogenic chemical produced in large quantity to make polycarbonates,
639 epoxy resins and thermal papers, which leads to its widespread presence in industrial and consumer
640 products and in the environment. Due to its endocrine disrupting properties, a great deal of scientific
641 research has been performed to examine the occurrence, concentration levels, transport, bioeffects and
642 fate of BPA in the environment. However, most of previous studies on risk assessment of BPA
643 pollution on the human and environmental health were based on BPA itself, the contributions of BPA
644 analogous derivative impurities and degradation intermediate products, which may possess similar or
645 even more harmful bioeffects on wildlife and humans, were not included. This article has provided a
646 review on the occurrence, estrogenic-related bioeffects and fate of BPA transformation products in
647 which the bisphenol structure has been preserved, and BPA impurities and co-pollutants identified in
648 previous studies. Special attention has been placed on BPA analogous derivatives. Some of the BPA
649 cleavage and rearrangement products and their endocrine activity and other biological effects have
650 been also discussed. Seventy-nine such BPA degradation intermediates and analogous derivatives have
651 been identified, five of them were found in effluents from paper recycling and water treatment plants as
652 well as other chlorination processes, sixty-three were BPA transformation intermediate products in
653 photo-degradation or other advanced oxidation processes, including ozonation, Fenton and photo-
654 Fenton reactions, ultrasonic treatment, sensitized and/or catalyzed photochemical and thermal chemical
655 processes, twenty-two were examined as impurities and co-pollutants in BPA products.

656 Among the BPA analogues and bisphenol intermediates of BPA degradation that have received
657 significant scrutiny, substantial evidence of endocrine disrupting activity and other adverse bioeffects

658 exists. It was found that chlorination of BPA usually increases its estrogenic disrupting activity and
659 toxicity. The agonist assay using the yeast two-hybrid system showed that 3,3'-diClBPA has an
660 estrogenic activity 38 times greater than BPA. Chlorinated BPA have also been found to have a greater
661 tendency to accumulate in human adipose tissue and a higher maternal transfer efficiency to newborns
662 than BPA. Several halogenated BPA products have been found to exhibit metabolic, obesogenic effects
663 and other biological activities not observed in BPA, such as thyroid hormonal activity. Hydroxylated,
664 quinone and other oxidized BPA derivatives generated in photodegradation, sonochemical processes,
665 ozonation and other advance oxidation, and biotransformation processes exhibit cytotoxic, genotoxic,
666 mutagenic and carcinogenic properties although most of them are less estrogenic than BPA. Several
667 BPA analogous impurities, such as 4-cumylphenol, show much higher human estrogen receptor α
668 (hERα) binding affinity and other harmful bioeffects than BPA. However, many of the published works
669 offer contradictory accounts regarding the nature of that activity, particularly around estrogen and
670 thyroid activity of the chlorinated BPA derivatives. Continued investigation will be necessary to
671 resolve these inconsistencies and provide a more complete picture of the hazards associated with BPA.

672 The review of the endocrine and other biological effects of the chemical transformation products,
673 analogous derivatives and impurities of BPA shows that the bioeffects of BPA itself represent an
674 incomplete summation of the hazards to human and environmental health resulting from the
675 widespread prevalence of BPA in the environment, in food and consumer products, and in drinking-
676 water infrastructure. A comprehensive risk assessment of BPA in the environment should consider also
677 the endocrine disrupting and other biological activities of BPA and its polymer degradation
678 intermediate products, impurities and co-pollutant analogous derivatives. Our current knowledge of
679 these chemicals is incomplete. Further research work is urgently needed to (1) develop more sensitive
680 and robust analytical and bioassay techniques for identification and characterization of BPA

degradation intermediate products and analogous derivatives, of their occurrence, distribution and transport in the environment; (2) To investigate the mechanisms and kinetics of the degradation of bisphenol derivatives and their transformation intermediates, and examine the persistence and fate of these analogous and transformation intermediate products in the environment, and determine their exposure risk to humans and ecosystems; (3) To better elucidate the mechanisms of endocrine disrupting and other hazardous biological activities from bisphenol transformation products and from coexposure to multiple bisphenol analogous and transformed derivatives along with other environmental pollutants. Most available toxicity tests are performed with a single bisphenol analog. In the environment, bisphenol derivatives and their transformation products usually occur as a mixture. The potential additive or synergistic effects generated by a mixture of bisphenol derivatives, their degradation products and other toxicants should also be considered in human and environmental health risk assessment.

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Graphical Abstract