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Review

Biodegradation or metabolism of bisphenol A: From microorganisms to mammals

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Abstract

Bisphenol A (BPA; 2,2-bis(4-hydroxyphenyl)propane; CAS Registry No. 80-05-7) is one of endocrine disruptors and is made by combining acetone and phenol. BPA can be metabolized by extensive organisms. In this review these BPA biodegradations or metabolisms by many organisms from microorganisms to mammals were referred. Though the metabolites of BPA can enhance estrogenicity or toxicity, generally, BPA metabolism by organisms leads to detoxication of BPA.

Keywords: Bisphenol A; Metabolism; Biodegradation; Toxic activity; Estrogenic activity

Contents

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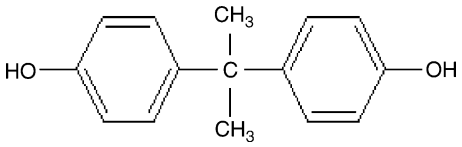

Fig. 1. Chemical structure of bisphenol A.

1. Introduction

Bisphenol A (BPA; 2,2-bis(4-hydroxyphenyl)propane; CAS Registry No. 80-05-7) is an organic compound composed of two phenol rings connected by a methyl bridge, with two methyl functional groups attached to the bridge (Fig. 1). BPA is known as one of endocrine disruptors (Krishnan et al., 1993) and has an acute toxicity to aquatic organisms in the range of 1–10 μg/ml for freshwater and marine species (Alexander et al., 1988).

BPA widely used as a material for the production of epoxy resins, phenol resins, polycarbonates, polyacrylates, polyesters and lacquer coatings on food cans (Staples et al., 1998). BPA can be leached from these plastic products and food- and drink-packaging. Especially, there are many reports on the contamination of BPA from canned food (Goodson et al., 2002; Kang and Kondo, 2003). The main factors influencing the migration of BPA from can surfaces are heating times and temperatures used in the manufacturing process (Munguia-Lopez and Soto-Valdez, 2001; Kang et al., 2003; Goodson et al., 2004).

Moreover, according to an increase in the use of products based on BPA, the possibility of environmental contamination by BPA has increased. High levels of BPA were identified from leachates of waste landfill (Yamada et al., 1999; Behnisch et al., 2001; Yamamoto et al., 2001; Filho et al., 2003). Yamamoto et al. (2001) reported that the levels of BPA in the leachates of hazardous waste landfill ranged from 1.3 to 17,200 ng/ml (average 269 ng/ml). The leaching of BPA from plastic wastes into water was also reported. The highest levels (9.8 and 139 μg/g) were identified from polyvinyl chloride products that use BPA as a stabilizer in their manufacturing process (Yamamoto and Yasuhara, 1999).

However, BPA can be biodegraded by microorganisms distributed in the environment. BPA can also be metabolized by enzymes existing in plants and animals. In this review these BPA biodegradations or metabolisms by many organisms from microorganisms to mammals were reviewed.

2. Bacteria

Many bacteria capable of biodegrading BPA have identified from soils (Sasaki et al., 2005), river waters (Ike et al., 2000; Kang and Kondo, 2002a,b; Kang et

Table 1
Microorganisms capable of biodegrading or metabolizing bisphenol A

Microorganisms	Strains	References
Bacteria	*Psudomonas paucimobilis* FJ-4	Ike et al. (2000)
	Pseudomonas sp.	Kang and Kondo (2002a)
	Pseudomonas putida	Kang and Kondo (2002a)
	Streptomyces sp.	Kang et al. (2004)
	Sphingomonas sp. strain AO1	Sasaki et al. (2005)
Fungi	*Pleurotus ostreatus* O-48	Hirano et al. (2000)
	Phanerochaete chrysosporium ME-446	Tsutsumi et al. (2001)
	Trametes versicolor IFO-7043	Tsutsumi et al. (2001)
	Trametes villosa	Fukuda et al. (2001), Uchida et al. (2001)
	Phanerochaete chrysosporum ME-446	Suzuki et al. (2003)
	Trametes versicolor IFO-6482	Suzuki et al. (2003)
	Aspergillus fumigatus	Yim et al. (2003)
	Fusarium sporotrichioides NFRI-1012	Chai et al. (2005)
	Fusarium moniliforme 2-2	Chai et al. (2005)
	Aspergillus terreus MT-13	Chai et al. (2005)
	Emericella nidulans MT-98	Chai et al. (2005)
	Stereum hirsutum	Lee et al. (2005)
	Heterobasidium insulare	Lee et al. (2005)
Planktons	*Chlorella fusca* var. *vacuolata*	Hirooka et al. (2003)
	Nannochloropsis sp.	Ishihara and Nakajima (2003)
	Chlorella gracilis	Ishihara and Nakajima (2003)

al., 2004) and wastewater treatment plants (Lobos et al., 1992; Spivack et al., 1994) (Table 1).

Wastewater treatment plants use bacteria to remove BPA from wastewater. Several studies reported that about >90% of BPA was removed between the influent and the effluent of a wastewater treatment process (Fürhacker et al., 2000; Staples et al., 1998). Nevertheless, the effluent containing BPA can be source of BPA contamination in the aquatic environment.

Bacteria capable of biodegrading BPA are distributed in river waters and half-lives for BPA biodegradation averaged below 5 days (Dorn et al., 1987; Jin et al., 1996; Ike et al., 2000; Klecka et al., 2001; West et al., 2001; Kang and Kondo, 2002a,b; Kang et al., 2004; Kang and Kondo, 2005). Though there are many bacteria capable of degrading BPA in river waters, however, bacteria with high BPA biodegradability are limited. Jin et al. (1996) reported that about 90% bacteria (40 out of 44) isolated from multiple sites of seven rivers could degrade BPA to a certain degree, but only six samples in 40 bacterial samples were able to do complete BPA biodegradation. Recently, Kang and Kondo (2002a) found that most bacteria (10 out of 11) isolated from three river waters had BPA biodegradability, but there were differences in removal rates of BPA (18–91%) and only two strains (a *Pseudomonas* sp. and a *Pseudomonas putida* strain) showed high BPA biodegradability (about 90%). Moreover, *Streptomyces* sp. strain isolated from river water has high BPA biodegradability (>90% for 10 days) (Kang et al., 2004). These bacteria with high BPA biodegradability may be useful for the fast purification of the aquatic environment contaminated by BPA.

Moreover, BPA biodegradation by bacteria is influenced by temperature and bacterial counts. Kang and Kondo (2002b) found that half-lives for BPA biodegradation in 15 river water samples averaged 4 and 7 days at 30 and 20 °C, respectively, but about 20% (0.04 mg/l) of BPA spiked was biodegraded at 4 °C for 20 days. In the case of bacterial counts, a study reported that a rate of BPA biodegradation in the group containing bacterial counts of >10,000 CFU/ml was faster than that in the group containing bacterial counts of <10,000 CFU/ml (Kang and Kondo, 2002b). However, Klecka et al. (2001) reported that BPA biodegradation did not correlate with bacterial counts. These differences may be due to the size of bacterial population that can do fast and complete BPA biodegradation or mineralization. Bacteria capable of doing complete BPA biodegradation or mineralization were isolated from river waters with high bacterial counts, but bacteria incapable of biodegrading BPA were found in river water with low bacteria counts (Jin et al., 1996).

Moreover, there is a significant difference of BPA biodegradation between under aerobic conditions and under anaerobic conditions. BPA in river waters has been biodegraded under aerobic conditions but not under aerobic conditions. Our previous study found that BPA in the spiked samples was rapidly biodegraded under aerobic conditions (>90%), but a decrease of BPA was hardly found under anaerobic conditions (<10%) for 10 days (Kang and Kondo, 2002a). Ronen and Abeliovich (2000) reported that BPA in the anaerobic slurry was not biodegraded even after 3 months of incubation. These results may mean that anaerobic bacteria have no or little BPA biodegradability. Moreover, BPA in anaerobic environment such as anaerobic marine sediment can persist for an extended period of time (Voordeckers et al., 2002).

Lobes' group (1992; Spivack et al., 1994) found the metabolism routes of BPA by bacteria by using a gram-negative bacterial strain MV1 isolated from the enriched sludge of BPA wastewater treatment plant. The MV1 strain utilized BPA as the sole carbon and energy source, and major and minor pathways of BPA metabolism were identified. The major pathway produced two primary metabolites, 4-hydroxyacetephenone and 4-hydroxybenzoic acid, and the minor pathway also produced two primary metabolites, 2,2-bis(4-hydrozyphenyl)-1-propanol and 2, 3-bis(4-hydroxyphenyl)-1, 2-propanediol. Moreover, they suggested from total carbon analysis for BPA that 60% of the carbon are mineralized to CO_2, 20% are associated with the bacterial cells and 20% are concerted to soluble organic compounds. On the other hand, Sasaki et al. (2005) suggested that the cytochrome P450 system is involved in BPA metabolism from a test using *Sphingomonas* sp. strain AO1. Moreover, microbial peroxidase can degrade BPA (Sakurai et al., 2001).

BPA metabolism by bacteria leads to no toxic and estrogenic effects of BPA. Ike et al. (2002) reported that only 4-hydroxyacetephenone among four metabolites showed a slighter estrogenic activity compared with BPA.

Interestingly, BPA in seawater than in river water can continue for longer time without biodegradation (about 30 days) (Ying and Kookana, 2003; Kang and Kondo, 2005). On BPA degradation in seawater, Ying and Kookana (2003) suggested that BPA may be degraded after a long acclimation period of bacteria to BPA (more than 30 days), but Kang and Kondo (2005) suggested that BPA in seawater may be caused by more chemical degradation than biological degradation, while organisms such as bacteria and flagellates can have an important effect on the chemical degradation of BPA.

3. Fungi

Many fungi can degrade BPA (Table 1), but fungi with high BPA degradability are also limited (Chai et al., 2005; Yim et al., 2003). For example, Chai et al. (2005) found that among 26 fungi strains, 11 strains could biodegrade BPA at >50% and four strains (*Fusarium sporotrichioides* NFRI-1012, *Fusarium moniliforme* 2-2, *Aspergillus terreus* MT-13 and *Emericella nidulans* MT-98) were more effective for BPA biodegradation.

BPA biodegradation by fungi is caused by mainly lignin-degrading enzymes such as manganese peroxidase (MnP) and laccase, which are produced by white rot basidiomycetes fungi (Hirano et al., 2000; Fukuda et al., 2001; Tsutsumi et al., 2001; Uchida et al., 2001; Suzuki et al., 2003). MnP is a heme peroxidase and oxidizes phenolic compounds in the presence of Mn(II) and H_2O_2. Laccase is a multicopper oxidase and catalyzes one-electron oxidation of phenolic compounds by reducing oxygen to water (Reinhammar, 1984). In the case of laccase, BPA metabolism is faster in the presence of mediators such as 1-hydroxybenxotriaxzole (HBT) and 2,2′-azino-bis(3-ethylbenzthiazoline-6-sulfonate) than in laccase alone. MnP and laccase can degrade BPA and remove its estrogenic activity (Hirano et al., 2000; Fukuda et al., 2001; Tsutsumi et al., 2001; Uchida et al., 2001; Suzuki et al., 2003; Lee et al., 2005).

Hirano et al. (2000) found that BPA by MnP was metabolized to phenol, 4-isopropenylphenol, 4-isopropylphenol and hexestrol. Uchida et al. (2001) suggested that the polymerization of BPA for forming oligomers is included in the step of BPA metabolism by laccase, followed by either the addition of phenol moieties or the degradation of the oligomers to release 4-isopropenylphenol. They also identified a BPA dimmer, 5,5′-bis-[1-(4-hydroxy-phenyl)-1-methyl-ethyl]-bisphenyl-2,2′-diol, from oligomers as a high molecular weight compound.

4. Planktons

The fact that algae have the potential possibility to remove various pollutants such as heavy metals was reported (Nagase et al., 1997). Algae use CO_2 as a carbon source and grow photoautotrophically. These characteristics mean low removal rates of pollutants under dark conditions. Recently, Hirooka et al. (2003, 2005) reported that the green alga *Chlorella fusca* var. *vacuolata* could biodegrade BPA and removed its estrogenic activity. *C. fusca* showed that the removal of BPA was 85% under light conditions for 120 h, but was 22% under dark conditions when 40 μM of BPA was added into medium (Hirooka et al., 2003). Monohydroxybisphenol A was identified as an intermediate of BPA biodegradation by *C. fusca* (Hirooka et al., 2005).

Ishihara and Nakajima (2003) reported that the recovery of BPA from medium was 13–34%, and was 25–53% from two phytoplankton marine algal cells (*Nannochloropsis* sp. and *C. gracilis*), respectively when the medium spiked with 40 μM of BPA was placed for 6 days under light conditions. In the case of zooplanktons such as *Arterima* sp. or *Brachionus* sp., however, the removal rate of BPA from the medium was ≤20%. On the other hand, over 40% of BPA was recovered from the zooplankton cells in the medium using a combination of the phyto and zooplankton, meaning that BPA was accumulated in the zooplankton cells through the phytoplankton cells.

5. Plants

BPA biodegradation by plants has examined using plant cell suspension cultures (Nakajima et al., 2002; Schmidt and Schuphan, 2002; Nakajima et al., 2004; Chai et al., 2003), plant enzymes (Sakurai et al., 2001; Xuan et al., 2002; Yoshida et al., 2002; Kang et al., in press), or using direct absorption of BPA into plants (Nakajima et al., 2002; Noureddin et al., 2004).

Plants can rapidly absorb BPA from water through their roofs and metabolize it to several glycosidic compounds. Nakajima et al. (2002) found that the BPA absorbed through root systems was metabolized to its β-glucoside and the metabolites were translocated to their leaves. On the other hand, Noureddin et al. (2004) suggested that BPA metabolites are detected as the BPA base at ca. 10% in the roots, some in the stems, but none in the leaves. These results show that the distribution of BPA and its metabolites in plant may be variable according to plant species.

Glycosylation of BPA is regarded as main route of metabolism of BPA in plants. The metabolites by glycosylation of BPA were well studied by Nakajima et al. (2004). They identified two major products, BPA mono-*O*-β-D-gentiobioside and the trisaccharide BPA mono-*O*-β-D-glucopyranosyl-(1 → 4)-[β-D-glucopyranosyl-(1 → 6)] β-D-glucopyranoside, and two minor products, mono- and di-*O*-β-D-glucopyranosides.

Moreover, the estrogenic activity was not found from these compounds, meaning that the glycosylation of BPA by plants lack the estrogenicity of the parent compound.

Enzymes of plants give an important effect on BPA biodegradation. Especially, two oxidative enzymes, peroxidase and polyphenol oxidase, are close relation with

Table 2
Enzymes capable of biodegrading or metabolizing bisphenol A

Enzymes	Sources	References
Manganese peroxidase (MnP)	Fungi (*Pleurotus ostreatus* O-48, *Phanerochaete chrysosporium* ME-446, *Trametes versicolor* IFO-7043, *Phanerochaete chrysosporum* ME-446 and *Trametes versicolor* IFO-6482)	Hirano et al. (2000), Tsutsumi et al. (2001), Suzuki et al. (2003)
Laccase	Fungi (*Phanerochaete chrysosporium* ME-446, *Trametes versicolor* IFO-7043, *Trametes villosa*, *Phanerochaete chrysosporum* ME-446 and *Trametes versicolor* IFO-6482)	Tsutsumi et al. (2001), Fukuda et al. (2001), Uchida et al. (2001); Suzuki et al. (2003)
Peroxidase	Bacteria (*Coprinus cinereus*), plant [soybean and horseradish (*Armoracia rusticana*)]	Sakurai et al. (2001), Caza et al. (1999), Sakuyama et al. (2003)
Polyphenol oxidase	Plant (mushroom)	Yoshida et al. (2002)
Cytochrome P450	Bacteria (*Sphingomonas* sp. strain AO1), mammals (mouse and rat)	Atkinson and Roy (1995a,b), Sakurai et al. (2001), Yoshihara et al. (2001)
UDP-glucuronosyltransferase (UGT)	Fish [carp (*Cyprinus carpino*)], mammals (mouse, rat and human)	Yokota et al. (1999, 2002), Cappiello et al. (2000), Matsumoto et al. (2002), Strassburg et al. (2002)
Sulfotransferase	Mammal (human)	Suiko et al. (2000), Nishiyama et al. (2002)

BPA metabolism (Caza et al., 1999; Yoshida et al., 2001, 2002; Sakuyama et al., 2003) (Table 2). In plants, generally, physiological stress, wounding, microbial or viral infection result in increased activity of polyphenol oxidase and peroxidase for self-protection (Vámos-Vigyázó, 1981). When crude enzymes prepared from vegetables and fruits were incubated with BPA, BPA was biodegraded by them (Xuan et al., 2002; Kang et al., in press). In the case of BPA biodegradation by plant enzymes, the pH and temperature exert an important influence on the oxidative removal of BPA (Caza et al., 1999; Xuan et al., 2002; Yoshida et al., 2001, 2002; Sakuyama et al., 2003; Kang et al., in press).

On the other hand, Yoshida et al. (2001, 2002) reported enzymatic oxidation of BPA to quinines by polyphenol oxidase from mushroom, but Endo et al. (2000) found no oxidation of BPA by polyphenol oxidase from mushroom. Yoshida et al. (2002) suggested that these different results may be caused by the use of different product. For example, they found that polyphenol oxidase from mushroom supplied by Worthingtom Biochemical could oxidize BPA to monoquinone, but polyphenol oxidase from mushroom supplied by Sigma did not oxidize BPA.

The main product of BPA obtained from the enzymatic oxygenation of polyphenol oxidase was the monoquinone derivative of BPA and small amount of bisquinone derivative was also identified (Yoshida et al., 2002). On the other hand, another study suggested that the oxidation products by potato enzyme were identified to be 4[1-(4-hydroxyphenyl)-1-methyl-ethyl]-benzene-1,2-diol and 4[1-(4-hydroxyphenyl)-1-methyl-ethyl]-benzene-1,3-diol. The BPA oxidized by plant enzymes lost the estrogenic activity (Xuan et al., 2002).

6. Animals

6.1. Invertebrates

There are very few available data for BPA biodegradation in invertebrates, while many data dealing with toxicity or estrogenic activity on invertebrates exit.

A study of toxicokinetics of BPA on freshwater clam *Pisidium amnicum* showed that half-lives for BPA at 1.8 and 11.6 °C were 221 and 43 h, respectively. The fast half-life for BPA with increasing temperature may be related to the elevated metabolic rate (Heinonen et al., 2002).

6.2. Vertebrates

6.2.1. Fish

In fish, two BPA metabolites (BPA sulfate and BPA glucuronic acid) were identified from zebrafish (*Danio rerio*) exposed to BPA. After 7 days of BPA exposure (100 μg/l), when zebrafish were transferred to clean ground water, within the first 2 h of the elimination phase, a rapid decrease in BPA and BPA sulfate concentrations was identified from 100 to 29.3% and from 100 to 29.4%, respectively. The final BPA and BPA sulfate concentrations were 10.4% of initial values and 4.6% after 168 h, respectively. On the other hand, BPA glucuronic acid

was from 100 to 67% after 2 h, reaching 7.5% after 7 days (Lindholst et al., 2003).

Yokota et al. (2002) reported an increase in UDP-glucuronosyltransferase (UGT) activities for BPA in microsomes prepared from carp (*Cyprinus carpino*) intestine. BPA was metabolized in the carp intestine mainly as BPA glucuronide. The UGT activity increased with carp development and reached its maximum level before the carp reaches sexual maturity (2 years old). In fish UGT activity is decreased at temperatures of >30 °C, but no loss of UGT activity at 25 °C (Yokota et al., 2002).

The metabolism levels of BPA may vary with fish species. For example, the metabolism of BPA was faster in the zebrafish liver than in the rainbow trout liver. A more rapid metabolism of BPA leads to the lower estrogenic sensitivity (Lindholst et al., 2001, 2003).

6.2.2. Birds

From an administration study of ^{14}C-BPA to quail embryos, strong labeling in the bile and the allantoic fluid was identified, meaning that BPA is metabolized and excreted by the embryos (Halldin et al., 2001). Generally, chicken embryos have a relatively high metabolic capacity during the first half of incubation, both in terms of cytochrome P450-catalysed reactions and conjugation (Dutton and Ko, 1966; Heinrich-Hirsch et al., 1990). In laying quail, ^{14}C-BPA administered orally and intravenously were rapidly removed via bile and excreted in feces (Halldin et al., 2001).

6.2.3. Mammals

In spite of differences in the route of administration, the administrated dose and the experimental animals, generally, free BPA is excreted in feces at the range of 56–82% and its metabolites are in urine at the range of 13–28% (Knaak and Sullivan, 1966; Yokota et al., 1999; Pottenger et al., 2000; Snyder et al., 2000).

BPA metabolism in mammary is two pathways, glucuronidation and sulfation of BPA. BPA is glucuronided by liver microsomes (Table 2). Yokota et al. (1999) reported that the glucuronidation was mediated by UGT2B1, an isoform of UGT, in the rat liver. The hepatic glucuronidation is slightly less in pregnancy than in nonpregnancy because multidrug resistance-associated protein II and UGT decrease in pregnancy (Inoue et al., 2004). Moreover, the UGT levels in the human fetal liver are lower than those in the adult liver (Cappiello et al., 2000; Matsumoto et al., 2002; Strassburg et al., 2002). Matsumoto et al. (2002) suggested that the activity of UGT toward BPA and its protein and mRNA contents are not detected in the fetal rat liver.

Moreover, microsomal cytochrome P450 enzymes in rat liver take part in the metabolism of BPA. Yoshihara et al. (2001) found that an inhibitor of the cytochrome P450 system, SKF 525-A, inhibited the metabolism of BPA. Cytochrome P450s can metabolize BPA into bisphenol-*o*-quinone via 5-hydroxy BPA and a bisphenol semiquinone (Atkinson and Roy, 1995a,b). On the other hand, BPA can inhibit human hepatic cytochrome P450s activities (Hanioka et al., 1998; Niwa et al., 2000; Pfeiffer and Metzler, 2004). In addition, the metabolites of BPA produced by microsomal cytochrome P450s showed the enhanced estrogenic (Yoshihara et al., 2001) or toxic activity such as DNA adduct formation with BPA metabolites (Atkinson and Roy, 1995a,b).

Sulfation of BPA by sulfotransferases in the liver is also included in the BPA metabolism pathway in mammary (Suiko et al., 2000; Nishiyama et al., 2002) (Table 2). Among human sulfotransferases, the simple phenol (P)-form phenol sulfotransferase (SULT1A1) (Suiko et al., 2000; Nishiyama et al., 2002) and thermostable phenol sulfotransferase (ST1A3) (Shimizu et al., 2002) showed the sulfation of BPA.

After glucuronidation or sulfation in the rat liver, the metabolites of BPA are excreted mainly into the bile (Inoue et al., 2001, 2004). However, more levels of metabolites are eliminated to the vein in pregnancy rats or in the female rats. The venous excretion of metabilites increases three-fold in pregnancy than in nonpregnancy (Inoue et al., 2004).

There are differences of species or strain in the metabolism of BPA. Negishi et al. (2004) reported that orally or subcutaneously administered BPA in primates (monkeys and chimpanzees) was more easily absorbed than in rats and it took longer time to eliminate BPA from serum in primates than in rats. Moreover, human liver microsomes can't glucuronidate BPA as extensively as the rat liver microsomes (Elsby et al., 2001b). The rate of BPA glucuronidation in rats is higher in the liver than in the intestine, but is opposite in fish (Yokota et al., 2002). On the other hand, in strain differences, Snyder et al. (2000) identified that F-344 rats excreted more BPA metabolites in urine than CD rats. Previous studies using Fischer 344 rats showed that BPA increased uterine epithelium (Steinmetz et al., 1997), pituitary prolactin secretion (Steinmetz et al., 1998), and DNA synthesis in vaginal epithelium (Long et al., 2000), but not in Sprague-Dawley rats. These differences may be caused by a difference in the metabolism activity for BPA between two strains.

In gender difference, the metabolism of BPA is faster in female rats than in male rats and the relative expression level of UGT2B1 mRNA is also higher in female

rats than in male rats (Takeuchi et al., 2004). However, the glucuronidation levels of BPA decrease in pregnancy (Inoue et al., 2004). Moreover, a continuous exposure to BPA leads to a decrease in the expression levels of UGT2B1 in male Wistar rats, but not in female rats (Shibata et al., 2002). Takeuchi and Tsutsumi (2002) suggested that gender differences in serum BPA concentrations of adult humans may be caused by differences in the androgen-related metabolism of BPA. In addition, Kim et al. (2003) reported higher levels of BPA glucuronide in men than in women, but levels of BPA sulfate were opposite. In Fisher 344 rats, female rats show higher concentration of both BPA glucuronide and BPA sulfate than male rats (Pottenger et al., 2000).

In BPA metabolites, BPA glucuronide is characterized as the major metabolite of BPA metabolism via liver microsome pathway. Other metabolites such as BPA sulfate conjugate, BPA diglucuronide, 5-hydroxy BPA and the corresponding sulfate conjugate were also reported (Atkinson and Roy, 1995a,b; Elsby et al., 2001a; Nakagawa and Suzuki, 2001; Shimizu et al., 2002). Jaeg et al. (2004) identified nine metabolites from the metabolism of BPA by CD1 mice liver microsomal and S9 fractions and these metabolites were isopropyl-hydroxyphenol, BPA glutathione conjugate, glutathionyl-phenol, glutathionyl 4-isopropylphenol and BPA dimers.

Toxicity and estrogenicity on BPA metabolites have been identified. Atkinson and Roy (1995a,b) found that the BPA metabolite, bisphenol-*o*-quinone, could bind DNA in vitro and in vivo. From these results, they suggested that covalent modifications in DNA by in vivo exposure of BPA may be a factor in the induction of hepatotoxicity. Moreover, Yoshihara et al. (2001) suggested that the estrogenicity of BPA increases (two to five times) through its biodegradation by rat liver S9 fractions, microsomal and cytosolic fractions. The active estrogenic metabolite was confirmed to be 4-methyl-2,4-bis(*p*-hydroxyphenyl)pent-1-ene (MBP) (Yoshihara et al., 2004). A recent study using medaka (*Oryzias latipes*) suggested that MBP has higher toxicity on its early life stages and shows about 250-fold higher estrogenic activity when compared with BPA (Ishibashi et al., 2005). In addition, BPA glucuronide has lower estrogenicity than BPA. The estrogenicity of 5-hydroxy BPA is also less than that of BPA, but it is known as a weak estrogenic compound (Nakagawa and Suzuki, 2001; Elsby et al., 2001a). The BPA sulfate shows no estrogenicity up to 1 mM, but an increase in levels of pS2 mRNA expression is found at a concentration of 1 μM of BPA (Shimizu et al., 2002).

7. Conclusions

BPA can be metabolized by many organisms from microorganisms to animals, but further studies of BPA metabolism on extensive organisms, especially, birds and invertebrates, are required. Though the metabolites of BPA can enhance estrogenicity or toxicity, generally, BPA metabolism by organisms leads to detoxication of BPA. However, the fact that BPA can be biodegraded or metabolized by organisms does not mean that BPA has no estrogenic or toxic effect on organisms.

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