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Review

Bisphenol A exposure, effects, and policy: A wildlife perspective

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ABSTRACT

Thousands of anthropogenic chemicals are present in the environment, and mounting evidence indicates that some have endocrine-disrupting effects in a variety of organisms. Of particular concern are chemicals that act as agonists or antagonists on vertebrate estrogen or androgen receptors. One such compound is bisphenol A (BPA), which appears to be both an estrogen receptor agonist and an androgen receptor antagonist. Used in the manufacture of plastic resins, BPA is found at low levels in surface-water, sediments, soils, and biota. Although it degrades quickly, it is pseudo-persistent in the environment because of continual inputs. Due to its environmental ubiquity, organisms may be exposed to BPA chronically or during sensitive life stages. While the impacts of BPA-related endocrine disruption in humans have been extensively studied, the endocrinal and systemic effects in wildlife are less well known. This article reviews the current state of knowledge of BPA inputs to the environment, routes of exposure, and effects on wildlife. We then critically examine the regulatory structure governing the environmental endpoints of BPA in the United States, European Union, and Canada, and discuss major challenges to the effective regulation of BPA. We conclude with a survey of treatment and mitigation options.

1. Introduction

Many of the thousands of anthropogenic chemicals currently released into the environment are endocrine-disrupting compounds (EDCs; Vandenberg et al., 2009). These are defined as exogenous chemicals or chemical mixtures that impact endocrine system structure or function and cause adverse effects (US Environmental Protection Agency, 2007). Endocrine systems regulate a multitude of developmental, metabolic, and reproductive processes including embryonic development, gonadal formation, sex differentiation, growth, and digestion. Endocrine-disrupting compounds may affect these processes by either binding to or blocking hormone receptors, thereby triggering or preventing hormonal response (Hotchkiss et al., 2008; Markey et al., 2001; Pedersen et al., 1999; Witorsch, 2002). Chemicals implicated in endocrine disruption include biocides, industrial compounds, surfactants, and plasticizers including bisphenol A (BPA) (Eskinazi et al., 2003; Falconer et al., 2006; Hayes et al., 2002; Markey et al., 2003; Renner, 1997).

Bisphenol A has become ubiquitous in the environment within the past 80 years because of its presence in a multitude of products including food and beverage packaging, flame retardants, adhesives, building materials, electronic components, and paper coatings (Staples et al., 1998). As demand for these products has increased, so has BPA production. In 1964, 42 metric tons of BPA were produced in the United States (Dermer, 1977). By 2003, global production of BPA was 3.2 million metric tons (Tsai, 2006), approximately one-third of which was manufactured in the United States (National Institute of Health, 2008). Global consumption of BPA in 2011 was predicted to exceed 5.5 million metric tons (Greiner et al., 2007).

Bisphenol A is a nonsteroidal xenoestrogen that exhibits approximately 10^{-4} the activity of estradiol (Witorsch, 2002). Estrogenic effects of BPA were first reported in 1936 (Dodds and Lawson, 1936) but its use as a synthetic estrogen was not pursued (Dodds et al., 1938). Recent work indicates that BPA may be as effective as estradiol in triggering some receptor responses (Stahlhut et al., 2009) and it may act as an androgen receptor antagonist (Roy et al., 2004; Urbatzka et al., 2007; Zoeller et al., 2005). While a considerable number of studies have been published on the effects of BPA exposure in experimental animals and in humans (e.g., vom Saal and Hughes, 2005; Willhite et al., 2008), relatively few studies have examined the effects of BPA on wildlife species in either laboratory or field settings.

Most studies of BPA effects on wildlife focus on endocrine systems; however, modes of action other than endocrine disruption

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may cause some observed effects (Barata et al., 2004; Hutchinson, 2002). At concentrations ranging from 1.1 to 12.8 mg/L, BPA is systemically toxic to various taxa, including daphnids (Alexander et al., 1988; Brennan et al., 2006; Hirano et al., 2004), mysids (Alexander et al., 1988; Hirano et al., 2004), and both freshwater (*Pimephales promelas*) and saltwater (*Menidia menidia*) fishes (Alexander et al., 1988). Based on reported EC50 and LC50 values that range from 1.0 to 10 mg/L (Environment Canada, 2008), BPA is classified as "moderately toxic" and "toxic" to aquatic biota by the European Commission and the United States Environmental Protection Agency (US EPA), respectively (Alexander et al., 1988; Commission of the European Communities, 1996). However, studies of BPA effects on wildlife indicate that the compound may be harmful even at environmentally relevant concentrations, which we define as 12 μg/L or lower (Table 1) (Kolpin et al., 2002; Lahnsteiner et al., 2005; Marcial et al., 2003; Oehlmann et al., 2006; Sohoni et al., 2001; Watts et al., 2003).

We summarize the properties, environmental compartments, and fates of BPA and then review the effects of BPA exposure on wildlife. From a wildlife-centered perspective, we examine the regulatory framework of BPA in the United States, the European Union, and Canada, and discuss some of the challenges to BPA regulation. We conclude with a discussion of treatment and mitigation options.

2. BPA environmental release, properties, compartments, and fates

Bisphenol A is a pseudo-persistent chemical, which despite its short half-life is ubiquitous in the environment because of continuous release (Oehlmann et al., 2009). Release can occur during chemical manufacture, transport, and processing. Post-consumer releases are primarily via effluent discharge from municipal wastewater treatment plants, leaching from landfills, combustion of domestic waste, and the natural breakdown of plastics in the environment (Crain et al., 2007; Kang et al., 2007; Kinney et al., 2006; Sidhu et al., 2005; US Environmental Protection Agency, 2010). In the United States, over 577 metric tons of BPA were reported as released during manufacture or processing in 2008 alone. Off-site transfers for incineration or to municipal wastewater treatment plants released another 1266 metric tons (US Environmental Protection Agency, 2010).

Formed by the condensation of phenol with acetone, BPA has a low vapor pressure, high melting point and moderate solubility (Cousins et al., 2002; Howard, 1989; Shareef et al., 2006). It is thus expected to have low volatility. Less than 1% of environmental BPA is thought to occur in the atmosphere, where it is believed to photo-oxidize and breakdown rapidly (Cousins et al., 2002; Howard, 1989). Based on reported log K_{OW} values that range from 2.20 to 4.16 (Dorn et al., 1987; Shao et al., 2007; Staples et al., 1998; Tsai, 2006; Yoon et al., 2003), BPA is considered to have low (Heinonen et al., 2002) or moderate (Cousins et al., 2002) hydrophobicity and thus a modest capacity for bioaccumulation. Based on these various characteristics, it is estimated that the largest environmental compartments of BPA are abiotic and are associated with water and suspended solids (~53%), soil (~25%), or sediments (~23%) (Cousins et al., 2002; Environment Canada, 2008; Staples et al., 1998).

2.1. BPA in water and suspended solids

Researchers were not aware that BPA could leach from plastics until 1993 (Krishnan et al., 1993) and subsequent studies confirmed that BPA can leach from polycarbonates and epoxy resins (Biles et al., 1997; Howdeshell et al., 2003; Takao et al., 2002; but see Mountfort et al., 1997). Many studies have since quantified BPA levels in various aqueous media, including fresh and marine surface waters, treatment plant influents and effluents, and groundwater (Table 1).

Surface-water concentrations of BPA vary considerably depending on the location, sampling period, and how the results are reported (Table 1). Observed surface-water concentrations of BPA in the United States range from 0.147 to 12 μg/L (Kolpin et al., 2002; Zhang et al., 2007). Crain et al. (2007) note that although BPA dissolved in surface water has a short half-life because of photo- and microbial degradation, metabolites may persist. Additionally, while most values reported for BPA in surface water are below 1 μg/L (Crain et al., 2007), BPA concentrations can vary with depth (Funakoshi and Kasuya, 2009) so sampling throughout the water column may be necessary to accurately characterize BPA.

Observed BPA concentrations in oceans and estuaries are relatively low compared to some freshwater systems (Table 1). However, BPA leaching could be a concern at marine sites where plastic waste has accumulated, as BPA leaches more rapidly in marine than in freshwater systems (Crain et al., 2007; Sajiki and Yonekubo, 2003) and microbial degradation may occur more slowly (Kang and Kondo, 2005). In addition, the bioavailable fraction of dissolved BPA may increase with salinity (Hu et al., 2006).

As with surface waters, BPA concentrations in effluents, leachate, and groundwater vary greatly (Table 1). Studies of wastewater treatment plants have shown both losses and gains of BPA as water moves through a treatment system (Al-Rifai et al., 2007; Fernandez et al., 2007; Loos et al., 2007; Vethaak et al., 2005). Effluent from municipal and mixed municipal-industrial wastewater treatment plants is a major source of environmental BPA (Crain et al., 2007) although reported BPA concentrations associated with these plants are generally lower than 1.5 μg/L (Table 1). However, one study of paper-mill effluent in Japan found mean and maximum BPA concentrations of 59 and 370 μg/L respectively (Fukazawa et al., 2002). The estimated half-life of BPA from manufacturing effluent is 2.5–4.0 days (Dorn et al., 1987), but common metabolites may persist for up to one month (Ike et al., 2000, 2006). Levels of BPA in landfill leachate can be very high; studies in Japan reported concentrations of 5400 μg/L (Yamada et al., 1999) and 17,200 μg/L (Yamamoto et al., 2001). Even when impacted by contaminant plumes, however, reported groundwater concentrations are generally low (Table 1) (Focazio et al., 2008; Latorre et al., 2003; Rudel et al., 1998).

2.2. BPA in sediments and soils

Studies in which both water and sediments were sampled report much higher BPA concentrations in the sediments than in the upper water column (Table 1). Funakoshi and Kasuya (2009) noted a strong correlation between BPA levels near the base of the water column and those in the sediment, which is consistent with observations of slow BPA biodegradation in anaerobic environments (Ike et al., 2006). With reported log K_{OC} values ranging from 2.50 to 4.5 (Ballard and Mackay, 2005; Fent et al., 2003; Heemken et al., 2001; Howard, 1989), BPA is thought to have a moderate affinity for soil organic matter and is therefore unlikely to be mobile or bioavailable in soils (Fent et al., 2003; Howard, 1989). However, mobility can be affected by soil chemistry and texture. Reports of increased BPA sorption in the presence of iron, cadmium, and lead are consistent but results conflict with regards to soil pH (Li et al., 2007; Zeng et al., 2006). Loffredo and Senesi (2006) documented rapid and complete desorption of BPA in sandy, acidic soils.

The primary source of BPA in soils is the land-application of sewage sludge or biosolids (Lemos et al., 2009). Reported levels of BPA in biosolids vary by many orders of magnitude, ranging from

Table 1
Observed environmental bisphenol A concentrations (μg/L unless otherwise indicated). "MDL": method detection limit; "RL": reporting limit; "n.d.": non-detected; "WWTP": wastewater treatment plant; "d.w.": dry weight.

Study number	Location	Max.	Mean	Range	MDL	Sample	Comment	Reference
Natural surface waters								
1	The Netherlands	21	0.14 (median)		0.011	River water	Observed in summer; following spring observed BPA concentration was <0.011	(Belfroid et al., 2002)
2	Japan	19				River water	Report by Ministry of Japan	(Crain et al., 2007)
3	USA	12			0.09 RL	River water	National reconnaissance	(Kolpin et al., 2002)
4	Portugal	5.03				River water	Monthly samples on multiple rivers	(Quiros et al., 2005)
5	Portugal	4.0	0.10	0.07–4.0	0.002	River water	Monthly samples on multiple rivers	(Azevedo et al., 2001)
6	The Netherlands	1.0	0.045 (median)	<0.0088–1.0		Surface water	Multiple marine, estuarine, and fresh surface waters	(Vethaak et al., 2005)
7	Japan	0.33		0.06–0.33	0.01	River water	Nagara River	(Funakoshi and Kasuya, 2009)
8	The Netherlands	0.320		<0.012–0.320	0.011	Marine waters		(Belfroid et al., 2002)
9	China	0.262		0.0025–0.262	0.001	River water	Quarterly samples	(Fu et al., 2007)
10	Japan	0.25			0.01	River water	Ibi River	(Funakoshi and Kasuya, 2009)
11	Italy	0.207			0.002	River water	Draining industrialized watershed	(Urbatzka et al., 2007)
12	Italy	0.175		0.036–0.175	0.002	River water	Multiple sites	(Loos et al., 2007)
13	The Netherlands	0.170		n.d.–0.170	0.011	River water		(Belfroid et al., 2002)
14	USA	0.147		n.d.–0.147	0.002	River water	Monthly samples	(Zhang et al., 2007)
15	China	0.0925		0.0015–0.0925	0.001	Estuarine water	Quarterly samples	(Fu et al., 2007)
16	Okinawa	0.08		n.d.–0.08	0.005	Estuarine and marine waters	Multiple marine and estuarine sites	(Kawahata et al., 2004)
17	Japan	0.058		0.036–0.058	0.005	Estuarine water	Multiple estuaries	(Kawahata et al., 2004)
18	Germany	0.014	0.0047	0.0005–0.014	0.00004	River water	Multiple rivers	(Kuch and Ballschmitter, 2001)
19	The Netherlands	0.012		n.d.–<0.012	0.011	Estuarine water		(Belfroid et al., 2002)
20	Germany	0.002	0.0011	0.0005–0.002	0.00002	Drinking water	Multiple drinking water sources	(Kuch and Ballschmitter, 2001)
21	South Korea		0.0025, 0.0029, 0.0043		0.001	River water	Two rivers sampled annually for three years	(Duong et al., 2010)
22	Italy		<0.001–0.145			Lagoon water	Mean values from multiple locations sampled monthly	(Pojana et al., 2007)
23	Belgium		0.016, 0.038, 0.042, 0.055		0.002	River water	Mean values from multiple rivers reported	(Loos et al., 2007)
Sediments and suspended solids (μg/kg d.w. unless otherwise indicated)								
24	The Netherlands	56	12 (median)	5.6–56		Suspended solids	Multiple marine, estuarine, and fresh surface waters	(Vethaak et al., 2005)
25	The Netherlands	43	3.2 (median)	<1.1–43		Sediment	Multiple marine, estuarine, and fresh surface waters	(Vethaak et al., 2005)
26	China	29.6 ng/L		2.5–29.6 ng/L		Suspended solids	Rivers, sampled quarterly	(Fu et al., 2007)
27	China	27.3		2.4–27.3		Sediment	Rivers, sampled quarterly	(Fu et al., 2007)
28	China	21.6 ng/L		0.8–21.6 ng/L		Suspended solids	Estuary, sampled quarterly	(Fu et al., 2007)
29	China	17.0		0.7–17		Sediment	Estuary, sampled quarterly	(Fu et al., 2007)
30	Okinawa	11		n.d.–11	0.5	Sediment	Multiple estuarine and marine sites	(Kawahata et al., 2004)
31	Japan	2.7		n.d.–2.7	0.5	Sediment	Multiple estuarine and marine sites	(Kawahata et al., 2004)
32	Italy		<2.0–118			Sediment	Multiple estuarine sites	(Pojana et al., 2007)
Pre-treatment and treated waters								
33	Japan	17,200	269 (median)	1.3–17,200	0.5	Landfill leachate	Hazardous-waste landfills	(Yamamoto et al., 2001)
34	Japan	5400		310–5400		Landfill leachate		(Yamada et al., 1999)
35	Japan	370	59	0.2–370		Paper-mill effluent	20 paper mills	(Fukazawa et al., 2002)

(*continued on next page*)

Table 1 (*continued*)

Study number	Location	Max.	Mean	Range	MDL	Sample	Comment	Reference
36	USA	1.7	0.82	0.11–1.7	0.0054	Untreated septage		(Rudel et al., 1998)
37	Canada	1.054		n.d.–1.054	0.0021	WWTP effluent	Multiple WWTPs	(Fernandez et al., 2007)
38	Canada	0.590		n.d.–0.590	0.0021	WWTP influent	Multiple WWTPs	(Fernandez et al., 2007)
39	USA	0.049			0.014	WWTP influent	Municipal	(Yu and Chu, 2009)
40	Canada	0.040	0.021	0.011–0.040	0.0021	Kraft mill effluent		(Fernandez et al., 2007)
41	Belgium	0.006			0.002	Textile mill effluent		(Loos et al., 2007)
42	Italy	0.005			0.002	WWTP effluent		(Loos et al., 2007)
43	Australia		23.02		0.01	WWTP influent	Combined municipal and industrial	(Al-Rifai et al., 2007)
44	Australia		5.48		0.01	WWTP influent	Combined sewage and stormwater	(Al-Rifai et al., 2007)
45	The Netherlands		1.410 (median)	0.250–5.625		WWTP effluent	Municipal	(Vethaak et al., 2005)
46	The Netherlands		0.575 (median)	<0.019–0.8		Industrial effluent		(Vethaak et al., 2005)
47	Australia		0.14		0.01	WWTP influent	Municipal	(Al-Rifai et al., 2007)
48	The Netherlands		0.118 (median)	<0.043–4.090		WWTP effluent		(Vethaak et al., 2005)
49	Belgium		0.028		0.002	WWTP effluent		(Loos et al., 2007)
50	Australia		n.d.		0.01	WWTP effluent	WWTPs treating different types of effluent	(Al-Rifai et al., 2007)
Groundwater								
51	USA	1.9		1–1.9	0.2	Groundwater	National reconnaissance	(Focazio et al., 2008)
52	Spain	1.5		0.05–0.18	0.01	Groundwater	Agricultural region, one heavily polluted sampling point	(Latorre et al., 2003)
53	USA	1.41	0.32	n.d.–1.41	0.0054	Groundwater	Impacted by landfill or septage leachate	(Rudel et al., 1998)
54	USA	0.029	0.016	n.d.–0.029	0.0054	Groundwater	Impacted by WWTP recharge	(Rudel et al., 1998)
Soils, sewage sludges, or biosolids (μg/kg d.w. unless otherwise indicated)								
55	USA	81				Soil amended with biosolid	Average of 3 replicate composite samples	(Kinney et al., 2008)
56	USA	147				Soil, unamended	Average of 3 replicate composite samples	(Kinney et al., 2008)
57	Canada	360				Sewage sludge, primary	Combined municipal and industrial WWTP	(Mohapatra et al., 2011)
58	Germany	1363		4–1363		Sewage sludge	39 sewage treatment plants; 2 analysis methods	(Fromme et al., 2002)
59	USA		4600			Biosolid	Average of 3 replicate composite samples	(Kinney et al., 2008)
60	Multiple	3.2×10^7		$0.1–3.2 \times 10^7$		Sewage sludge	Review of organic chemicals in sewage sludges	(Harrison et al., 2006)

0.10 to 3.2×10^7 μg/kg dry weight (Fromme et al., 2002; Harrison et al., 2006 and references therein; Kinney et al., 2008; Mohapatra et al., 2011). Annually, an estimated 4×10^6 and 2.4×10^6 dry tons of biosolids are applied in the United States and Europe, respectively, primarily to agricultural fields (Kinney et al., 2008). Given these rates, BPA inputs to terrestrial ecosystems may be substantial, despite potentially low BPA levels in biosolids. The half-life of BPA in soils has been estimated as 3 days (Fent et al., 2003), 7 days (Ying and Kookana, 2005), and 37.5 days (Environment Canada, 2008). No degradation was observed in anaerobic soils after 70 days (Ying and Kookana, 2005) or in anoxic estuarine sediments after 120 days (Voordeckers et al., 2002). Bisphenol A presence in soils may constitute a significant concern (Lemos et al., 2009), although data on BPA levels in soils and in edaphic organisms are sparse (but see Kinney et al., 2008; Lemos et al., 2009).

2.3. BPA in biota

Compared to non-biotic environmental compartments, relatively little environmental BPA occurs in biota. Published bioconcentration factor (BCF) values for BPA are well below 1000, which the US EPA considers to be the threshold for concern. Reported BCFs for fish exposed to BPA range from <20 to 68 (Staples et al., 1998). A study of boreal freshwater clams (*Pisidium amnicum*) exposed to environmentally relevant BPA concentrations and temperatures found temperature-dependent BCFs that ranged from 110 to 144 (Heinonen et al., 2002). At low doses, BPA is biodegraded or metabolized, so bioaccumulation generally occurs only with high doses (Kang et al., 2007; Pritchett et al., 2002; Staples et al., 1998). Like BPA, some of its metabolites are xenoestrogens. For example, a study of medaka (*Oryzias latipes*) found that the BPA metabolites 4,4′-dihydroxy-α-methylstilbene and 4-methyl-2,4-bis(4-hydroxyphenyl)pent-1-ene

stimulated levels of estrogenic activity exceeding that of BPA by 40- and 300-fold, respectively (Yamaguchi et al., 2005).

3. Effects of BPA on wildlife

Attempts to quantify the effects of BPA exposure on wildlife face a number of challenges. First, such effects have been reported for a wide variety of wildlife species but generally at high BPA concentrations (Crain et al., 2007; Hotchkiss et al., 2008; Oehlmann et al., 2009). Further, the complexities of natural systems, which include spatially varying exposure levels (Hotchkiss et al., 2008), chemical mixtures, and trophic interactions, mean that relatively few studies have investigated the effects of chemical exposure on wildlife *in situ*. In addition, susceptibility to endocrine disruption varies temporally, with increased risk occurring during critical developmental windows. Most toxicological studies of BPA have therefore been laboratory trials using model organisms, and this increases the difficulty of accurately predicting wildlife responses to environmentally relevant BPA concentrations. Finally, many BPA toxicity studies have used endocrine-related measurement endpoints. Sub-lethal effects may also be triggered by other toxicological modes of action; accurately identifying these mechanisms may be necessary in order to characterize cumulative organismal response to environmental toxicity (Barata et al., 2004; Hutchinson et al., 2009).

3.1. Invertebrates

Invertebrates are frequently used as bioindicators in EDC studies both *in situ* and in the laboratory. Research suggests that some invertebrates appear to be quite sensitive to BPA, and effects have been documented at environmentally relevant concentrations (Oehlmann et al., 2009). However, scientists question whether invertebrate estrogen receptors function similarly to those in vertebrates (Brennan et al., 2006). As a result, it is unclear whether BPA toxicity in these organisms occurs through the endocrine system or other mechanisms (Hutchinson, 2002).

Several studies have observed developmental effects in invertebrates at various exposure levels (Table 2, Fig. 1). Both midge (*Chironomus riparius*) larvae and the marine copepod *Tigriopus japonicus* showed developmental inhibition at very low concentrations of BPA (0.08 and 0.1 μg/L respectively) (Marcial et al., 2003; Watts et al., 2003). However, it is unclear if these effects have any long-term impacts. Higher exposure (11.4 μg/L BPA for one hour) caused premature larval metamorphosis and settlement in the marine polychaete worm *Capitella capitata* (Biggers and Laufer, 2004). Likewise, BPA concentrations of 12.5–60 μg/L stimulated larval development in *T. japonicus* (Mariager, 2001; Oehlmann et al., 2009). In contrast, the copepod *Acartia tonsa* exhibited developmental inhibition at BPA concentrations above environmentally relevant levels (100 μg/L) (Andersen et al., 1999). Even higher concentrations of BPA exposure (>300 μg/L) resulted in developmental arrest and mortality in the sea urchin *Paracentrotus lividus* (Arslan and Parlak, 2008). At extremely high exposures (16,000–80,000 μg/L), abnormal growth and inhibition of gemule germination was found in freshwater sponges *Heteromyenia* sp. and *Eunapius fragilis* (Hill et al., 2002). Extremely high exposures (10,000 μg/kg–1,000,000 μg/kg soil) also resulted in reduced time to molt and decreased overall growth in the terrestrial isopod *Porcellio scaber* (Lemos et al., 2009, 2010a). Protein over-expression in the hepatopancreas, gut, and testes was also found at 10,000 μg/kg soil in *P. scaber* (Lemos et al., 2010b).

Studies of reproductive effects due to BPA exposure have also been conducted for a variety of invertebrates (Table 2). In the freshwater ramshorn snail (*Marisa cornuarietis*), exposure levels >1.0 μg/L were found to result in superfeminization (additional female organs, enlarged sex glands, oviduct deformities, and increased fecundity), oviduct rupture, and mortality (Oehlmann et al., 2000) (Fig. 1). In the mollusc *Mytilus edulis*, spawning induction, as well as oocyte and ovarian follicle damage, was observed following BPA exposure for 3 weeks at 50 μg/L (Aarab et al., 2006). In the marine copepod *A. tonsa*, reduced egg production, reduced hatch success of offspring from exposed adults, and increased offspring mortality was found at exposures exceeding environmentally relevant concentrations (>100 μg/L) (Andersen et al., 1999). Similarly, in the sea urchin *Paracentrotus lividus* a 30-min BPA exposure (300 μg/L) reduced fertilization success approximately 42%, and increased larval deformities in the offspring of BPA exposed sperm (Arslan and Parlak, 2008). In soils, female *P. scaber* exhibited increased miscarriages and reduced reproductive allocation following 10,000 μg/kg soil exposure (Lemos et al., 2010c). Juvenile *P. scaber* exhibited female-biased sex ratios after exposure at the same level (Lemos et al., 2009).

While developmental and reproductive effects in invertebrates have been reported due to BPA exposure, many were observed at levels currently well above environmentally relevant concentrations. However there are a few notable exceptions (Table 2, Fig. 1). The effect of BPA appears to vary considerably among related taxa, and it appears that some invertebrates may be hypersensitive to BPA exposure (freshwater molluscs and insect larvae, and marine copepods in particular).

3.2. Fish

Due to cost effectiveness, ease of maintaining broodstock for large-scale studies, and likelihood of exposure, several fish species are currently utilized as model systems for endocrine disruption assays. Species commonly used include fathead minnow (*Pimephales promelas*), Japanese medaka (*O. latipes*), zebrafish (*Danio rerio*), and rainbow trout (*Oncorhynchus mykiss*) (Hotchkiss et al., 2008; Lindholst et al., 2003). While BPA exposure has resulted in growth and developmental effects in fishes, this has only been found to occur above typical environmental levels (Table 2). Alo et al. (2005) found 80 μg/L BPA altered the activity of neural estrogen receptors that regulate growth hormone in Mediterranean rainbow wrasse (*Coris julis*), potentially impairing reproduction and development in this sequentially hermaphroditic species. Embryonic medaka were found to exhibit increased morphological deformities from 200 μg/L BPA exposure (Pastva et al., 2001), whereas zebrafish embryos exposed to 228 μg/L concentrations of BPA showed signs of feminized brains (Crain et al., 2007). At higher BPA exposure (1000 μg/L) yolk sac edema and hemorrhage were observed in salmon fry (*Salmo salar m. Sebago*) (Honkanen et al., 2004).

BPA exposure has also been found to result in reproductive effects in fish, even at environmentally relevant levels (Table 2, Fig. 1). Fathead minnows exhibited altered sex cell type ratios (increased percentage of spermatocytes) following 1 μg/L BPA exposure, and reduced numbers of mature spermatozoa at 16 μg/L (Sohoni et al., 2001). Gonad structural changes in male carp and an increase in oocyte atresia in female carp have been documented after 1 μg/L BPA exposure (Mandich et al., 2007). Lahnsteiner et al. (2005) observed reduced sperm quality and delayed ovulation in brown trout (*Salmo trutta f. fario*) following BPA exposure (≥1.75 μg/L), while complete inhibition of ovulation was observed at 5 μg/L BPA. Altered sex steroid levels were also found in the marine turbot (*Psetta maxima*) after exposure to BPA concentrations of 59 μg/L (Labadie and Budzinski, 2006). These changes can affect growth, bone and brain development, cellular division, and cause masculinization or feminization (Oehlmann et al., 2009).

Table 2
Comparison of laboratory/toxicity studies of bisphenol A effects on wildlife.

Study number	Species	BPA exposure (μg/L)	Effect	Citation
Invertebrates				
1	Annelid (*Capitella capitata*)	11.4 μg/L for 1 h	Premature metamorphosis of larvae	(Biggers and Laufer, 2004)
2	Cnidarian (*Hydra vulgaris*)	42 μg/L for 6 weeks	Tentacle damage & contracted bodies	(Pascoe et al., 2002)
3	Crustacean (*Acartia tonsa*)	100 μg/L for 2 weeks	Developmental inhibition	(Andersen et al., 1999)
4	Crustacean (*Acartia tonsa*)	12.5 μg/L for 3 weeks	Developmental stimulation	(Mariager, 2001; Oehlmann et al., 2009)
5	Crustacean (*Gammarus fossarum*)	50 μg/L for 103 days	Accelerated oocyte development & decreased number of offspring	(Schirling et al., 2006)
6	Crustacean (*Tigriopus japonicas*)	0.1 μg/L for 4 weeks	Developmental inhibition	(Marcial et al., 2003)
7	Echinoderm (*Hemicentrotus pulcherrimus* & *Strongylocentrotus nudus*)	228 μg/L for 48 h	Suppressed development	(Kiyomoto et al., 2006)
8	Echinoderm (*Paracentrotus lividus*)	300 μg/L for 30 min	42% reduction in fertilization & increased larval deformities	(Arslan and Parlak, 2008)
9	Insect (Chironomid larvae)	0.08 μg/L – time not specified	Delayed larval emergence	(Watts et al., 2003)
10	Isopod (*Porcellio scaber*)	10,000 μg/kg for 16 weeks	Reduced time to molt & altered sex ratios	(Lemos et al., 2009)
11	Isopod (*Porcellio scaber*)	10,000 μg/kg for 10 weeks	Reduced overall growth	(Lemos et al., 2010a)
12	Isopod (*Porcellio scaber*)	10,000 μg/kg for 15 days	Identifiable protein expression changes	(Lemos et al., 2010b)
13	Isopod (*Porcellio scaber*)	10,000 μg/kg for 56 days	20% miscarriage rate & reduced reproductive allocation	(Lemos et al., 2010c)
14	Mollusc (*Mytilus edulis*)	50 μg/L for 3 weeks	Spawning induction, oocyte & ovarian follicle damage	(Aarab et al., 2006)
15	Mollusc (*Mytilus edulis*)	59.4 μg/L for 3 weeks	Identifiable protein expression changes	(Apraiz et al., 2006)
16	Mollusc (*Marisa cornuarietis*)	1.0 μg/L for 5 months	Superfeminization, oviduct rupture, & mortality	(Oehlmann et al., 2006)
17	Mollusc (*Potamopyrgus antipodarum*)	5 μg/L for 9 weeks	Increased female fecundity	(Jobling et al., 2003)
18	Mollusc (*Potamopyrgus antipodarum*)	≤640 μg/L for 12 weeks	No effect	(Forbes et al., 2007)
19	Mollsuc (*Potamopyrgus antipodarum*)	0.19 μg/kg for 4 weeks	Increased female fecundity	(Duft et al., 2003)
20	Nematode (*Caenorhabditis elegans*)	10^{-9} M BPA agar for 6 days	Increased number of germ cells	(Hoshi et al., 2003)
21	Nematode (*Caenorhabditis elegans*)	0.1 μM BPA agar for 24 h	Reduced feeding behavior	(Kohra et al., 2002)
22	Sponge (*Heteromyenia* sp. & *Eunapius fragilis*)	16 PPM for 9 days	Morphological deformities	(Hill et al., 2002)
Fish				
23	Atlantic Cod (*Gadus morhua*)	50 μg/L for 3 weeks	Vtg induction	(Larsen et al., 2006)
24	Atlantic Salmon (*Salmo salar m. sebago*)	1000 μg/L for 6 days	Yolk sac edema & hemorrhage	(Honkanen et al., 2004)
25	Brown Trout (*Salmo trutta f. fario*)	1.75 μg/L for ~3 ½ months	Reduced sperm quality & delayed ovulation	(Lahnsteiner et al., 2005)
26	Brown Trout (*Salmo trutta f. fario*)	5 μg/L for ~3 ½ months	Complete inhibition of ovulation	(Lahnsteiner et al., 2005)
27	Carp (*Cyprinus carpio*)	1 μg/L for 2 weeks	Gonad structural changes in males & increased oocyte atresia	(Mandich et al., 2007)
28	Carp (*Cyprinus carpio*)	1–10 μg/L for 2 weeks	Decrease estrogen to androgen ratios in blood	(Mandich et al., 2007)
29	Carp (*Cyprinus carpio*)	100 μg/L for 2 weeks	Vtg induction	(Mandich et al., 2007)
30	Carp (*Cyprinus carpio*)	1000 μg/L for 2 weeks	Increase estrogen to androgen ratios in blood	(Mandich et al., 2007)
31	Carp (*Cyprinus carpio*)	1000 μg/L for 2 weeks	Intersex condition	(Mandich et al., 2007)
32	European Seabass (*Dicentrarchus labrax*)	10 μg/L for 2 weeks	Vtg induction	(Correia et al., 2007)
33	Fathead Minnow (*Pimephales promelas*)	1 μg/L for 164 days	Increased percentage of spermatocytes	(Sohoni et al., 2001)
34	Fathead Minnow (*Pimephales promelas*)	16 μg/L for 164 days	Reduced numbers of mature spermatozoa	(Sohoni et al., 2001)
35	Fathead Minnow (*Pimephales promelas*)	160 μg/L for 2 weeks/164 days	Vtg induction	(Brian, 2005; Sohoni et al., 2001)
36	Goldfish (*Carassius auratus*)	40 μg/L for 4 weeks	Vtg induction	(Ishibashi et al., 2001)
37	Guppy (*Poecilia reticulate*)	274 μg/L for 3 weeks	Reduced sperm counts	(Haubruge et al., 2000)
38	Longchin Goby (*Chasmichthys dolichognathus*)	0.1 μg/L - time not specified	Inhibit estrogen synthesis	(Baek et al., 2003)
39	Longchin Goby (*Chasmichthys dolichognathus*)	0.44 nM for 38 h	Stimulated germinal vesicle breakdown	(Baek et al., 2007)
40	Medaka (*Oryzias latipes*)	200 μg/L for 9 days	Embryonic deformities	(Pastva et al., 2001)
41	Medaka (*Oryzias latipes*)	837 μg/L for 3 weeks	Intersex condition	(Kang et al., 2002)
42	Mediterranean Rainbow Wrasse (*Coris julis*)	80 μg/L for 2 weeks	Altered binding activity of neural estrogen receptors	(Alo et al., 2005
43	Rainbow Trout (*Oncorhynchus mykiss*)	500 μg/L for 1 week	Vtg induction	(Lindholst et al., 2003
44	Turbot (*Psetta maxima*)	59 μg/L for 2 weeks	Altered sex steroid levels	(Labadie and Budzinski, 2006)
45	Zebrafish *(Danio rerio)*	228 μg/L for 48 h	Feminized brains in embryos	(Crain et al., 2007)
46	Zebrafish (*Danio rerio*)	1000 mg/kg of body mass- time not specified	Female skewed sex ratios in fry	(Crain et al., 2007)
47	Zebrafish (*Danio rerio*)	534 μg/L for 1 week	Vtg induction	(Lindholst et al., 2003)

Table 2 (*continued*)

Study number	Species	BPA exposure (μg/L)	Effect	Citation
Amphibians				
48	African Clawed Frog (*Xenopus laevis*)	20 μM *BPA* concentration larval stages 6–10	Malformations and apoptosis in central nervous system	(Oka et al., 2003)
49	African Clawed Frog (*Xenopus laevis*)	22.8 μg/L for 36 h	Vtg induction	(Kloas et al., 1999)
50	African Clawed Frog (*Xenopus laevis*)	22.8 μg/L for two weeks	Sex reversal male to female	(Levy et al., 2004)
51	African Clawed Frog (*Xenopus laevis*)	22.8 μg/L for 12 weeks	Female-biased sex ratio	(Kloas et al., 1999)
52	African Clawed Frog (*Xenopus laevis*)	4600 μg/L for 93 h	Abnormal gut coiling, edema, microcephaly, and decreases in body length	(Sone et al., 2004)
53	African Clawed Frog (*Xenopus laevis*)	0.83, 2.1, 9.5, 23.8, 100 and 4971 μg/L for 90 days	No effect	(Pickford et al., 2003)
54	African Clawed Frog (*Xenopus laevis*)	5700 μg/L	Head malformations, scoliosis, and organogenesis suppression occur	(Iwamuro et al., 2003)
55	Dark Spotted Frog (*Rana nigromaculata*)	200 μg/L for 45 days	Tail flex malformations	(Yang et al., 2005)
56	European Common Frog (*Rana temporaria*)	100 μM BPA	No Vtg induction	(Rankouhi et al., 2005)
57	Western Clawed Frog (*Silurana tropicalis*)	2.28 μg/L for nine days	Spontaneous metamorphosis inhibited	(Kashiwagi et al., 2008)
58	Wrinkled Frog (*Rana rugosa*)	10^{-7} M for nine days	Tail regression suppressed	(Goto et al., 2006)
Reptiles				
59	Broad-snouted Caiman (*Caiman latirostris*)	1.4 ppm (90 μg/egg)	Abnormal seminiferous tubules in males	(Stoker et al., 2003)
60	Broad-snouted Caiman (*Caiman latirostris*)	140 ppm (9 mg/egg)	100% male to female sex reversal	(Stoker et al., 2003)
Birds				
61	Japanese Quail (*Coturnix japonica*)	67 and 200 μg/g per egg,	No effect	(Halldin et al., 2001)
62	Japanese Quail (*Coturnix japonica*)	200 μg/g per egg	Oviduct abnormalities in females	(Berg et al., 2001)
63	White Leghorn Chicken	2 μg/kg of BPA every two days for maximum of 23 weeks	Delayed growth of the male chicken phenotype including the comb, wattle and testes	(Furuya et al., 2006)
64	White Leghorn Chicken	200 μg/g per egg	Feminization of the left testes in male chickens	(Berg et al., 2001)
65	White Leghorn Chicken	200,000 μg of BPA orally every week for 14 weeks	Males reduced weight in combs and testes	(Furuya et al., 2002)
Mammals				
66	Euroean Polecat (*Mustela putorius*)	250 mg/kg/day	No effect	(Nieminen et al., 2002b)
67	Field Vole (*Microtus agrestis*)	250 mg/kg/day	Increased testosterone levels	(Nieminen et al., 2002a)

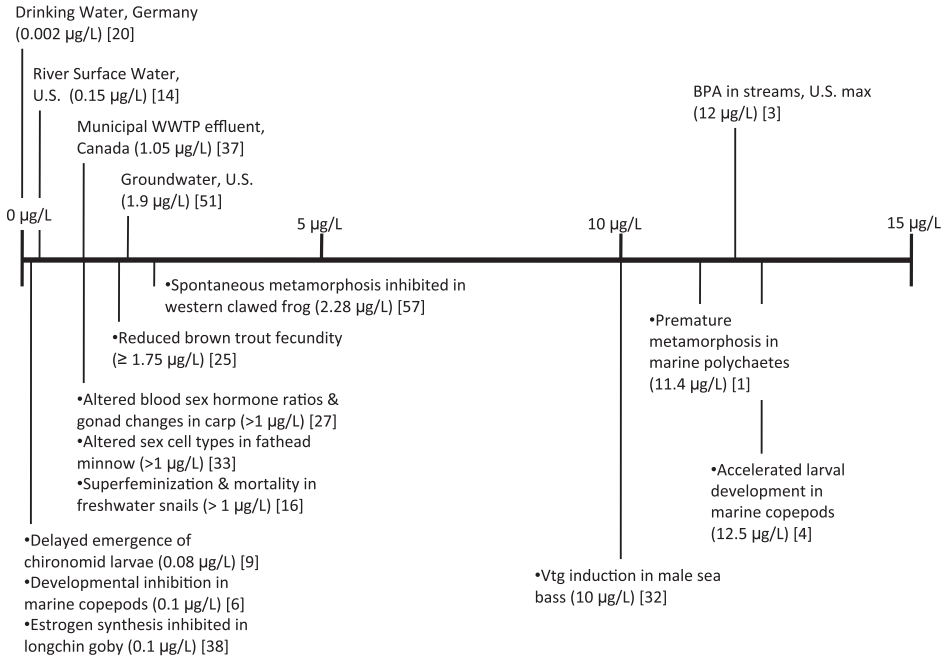

Fig. 1. Scale-bar of wildlife effects at environmentally relevant concentrations of bisphenol A. Values on the top half of the scale represent measured BPA concentrations in U.S. and international aquatic ecosystems; bracketed numbers refer to references in Table 1. Values on the bottom half represent wildlife effects observed in various studies; bracketed numbers refer to references in Table 2.

At BPA concentrations above environmentally relevant levels (274 μg/L) male guppies (*Poecilia reticulata*) had reduced sperm counts (Haubruge et al., 2000). Higher BPA levels (837 and 1000 μg/L) caused intersex condition in medaka and carp (Kang et al., 2002; Mandich et al., 2007).

One commonly used biomarker for vertebrate exposure to estrogenic compounds is the egg yolk protein precursor vitellogenin (Vtg), which is easily identified in blood samples (Crain et al., 2007; Oehlmann et al., 2009). Males exposed to BPA readily express Vtg; yet it is undetectable in unexposed males. The presence of Vtg proteins in male fish can indicate feminization or intersex condition that may result in reduced fecundity. Induction of Vtg proteins due to BPA has been found in numerous fishes, although lowest observed effect concentrations (LOECs) are generally above environmental levels. Male goldfish (*Carassius auratus*) exhibited increased Vtg concentrations following BPA exposures above 40 μg/L (Ishibashi et al., 2001). Male carp and fathead minnows exhibited Vtg induction following higher BPA exposures of 100 μg/L and 160 μg/L, respectively (Brian, 2005; Mandich et al., 2007; Sohoni et al., 2001). However, a study by Correia et al. (2007) found that environmentally relevant BPA concentrations (10 μg/L) induced Vtg in juvenile seabass (*Dicentrarchus labrax*). Variation in Vtg induction across taxa is likely due to species-specific ED binding affinities, metabolic rates, or study design differences (Crain et al., 2007).

Bisphenol A is also known to have epigenetic effects, such as altered patterns of gene expression in estrogen signaling pathways, which have been reported in fishes including carp and killifish (*Kryptolebias marmoratus*) (Lee et al., 2007; Moens et al., 2006; Seo et al., 2006). The observed gene expression patterns are specific to BPA, suggesting gene expression assays may be a useful tool for detecting BPA in the aquatic environment. However, direct effects on reproduction or survival due to gene expression alterations are currently unknown.

3.3. Amphibians

Amphibian eggs and larvae are thought to be particularly sensitive to BPA (Iwamuro et al., 2003). As amphibians have highly permeable skin and remain in aquatic habitats through critical hormone-regulated developmental stages, there is some concern that endocrine disruptors could be playing a role in amphibian declines (Hayes et al., 2002). At environmentally relevant levels of BPA, adverse effects are observed at metamorphosis (Table 2, Fig. 1). In the western clawed frog (*Silurana tropicalis*) for instance, BPA was found to inhibit spontaneous metamorphosis after nine days at concentrations of 2.28 μg/L (Kashiwagi et al., 2008). As metamorphosis is controlled by circulating thyroid hormones, this suggests that BPA can act as a thyroid hormone antagonist (Kashiwagi et al., 2008). However, an African clawed frog (*Xenopus laevis*) larvae study by Pickford et al. (2003) examining concentrations from 0.83 to 4971 μg/L over a 90-day period, found no observable effects. Multiple studies have also looked at sex ratio changes induced by BPA exposure. A study by Levy et al. (2004), also on African clawed frog larvae, found that exposure to 22.8 μg/L for two weeks resulted in complete sex reversal from male to female. Kloas et al. (1999) reported that African clawed frog larvae exposed to 22.8 μg/L BPA for 12 weeks resulted in a female-biased sex ratio change. In the Japanese pond frog *(Rana nigromaculata*), tadpoles exposed to BPA concentrations of 200 μg/L for 45 days resulted in tadpole tail flexure malformations (Yang et al., 2005). At higher concentration of BPA, 4600 μg/L for 93 days, exposed African clawed frog embryos experienced abnormal gut coiling, edema, microcephaly, and decreases in body length (Sone et al., 2004). Even higher levels (5700 μg/L) resulted in head malformations, scoliosis, and organogenesis suppression (Iwamuro et al., 2003).

In adult studies, African clawed frog liver cells exposed to BPA at a concentration of 22.8 μg/L for 36 h increased vitellogenin-mRNA accumulation in male frogs (Kloas et al., 1999). Similar results were found for fire-bellied toads (*Bombina orientalis*) (Gye and Kim, 2005). However, a study on the brown frog (*Rana temporaria*) showed no changes in Vtg for BPA concentrations up to 22,800 μg/L (Rankouhi et al., 2005).

3.4. Reptiles

Reptiles have also shown negative effects when exposed to BPA. In species that have temperature-dependent sex determination, such as the broad-snouted caiman (*Caiman latirostris*), BPA has been shown to induce sex changes in embryos. Stoker et al. (2003) found that BPA exposure of 1400 μg/L (90 μg/egg) resulted in abnormal seminiferous tubules. When eggshells were exposed to higher amounts of BPA (140,000 μg/L (9 mg/egg)) during critical periods for gender determination, Stoker et al. (2003) noted complete sex reversal from male to female in eggs incubated at the male-determining temperature. Such malformations and sex reversals have the capacity to lower reproductive success. Where BPA contamination is suspected, a skewed sex ratio in temperature-dependent sex determination species could be used as an indicator of environmental health (Crain and Guillette, 1998).

3.5. Birds

Few studies investigating the effects of BPA on birds have been published to date, and only one has shown effects at environmentally relevant levels (Table 2). Berg et al. (2001) found increased mortality in chicken (*Gallus domesticus*) embryos and that male embryos experienced feminization of the left testes when eggs were injected with a single dose of 200 μg BPA/g egg early in incubation. Furuya et al. (2002) reported delayed growth of comb, wattle, and testes in male chickens that received oral doses of BPA as low as 2 μg/1000 g body weight every two days for up to 23 weeks. The same study found no difference between controls and juvenile chickens fed high doses of BPA (200,000 μg/1000 g body weight) weekly from 2 to 16 weeks of age. However, chickens receiving BPA exhibited reduced weight of combs and testes, with the latter organs containing smaller seminiferous tubules and exhibiting limited spermatogenesis. The authors suggest that an endocrine-disrupting mechanism might trigger these effects and that reproduction was likely to be impaired (Furuya et al., 2002).

Estrogen-like effects have also been reported in Japanese quail (*Coturnix japonica*). Unlike chickens in the same study, quail eggs injected with 200 μg of BPA/g egg were found to produce females with oviduct abnormalities (Berg et al., 2001). Halldin et al. (2001), however, found that quail eggs with BPA exposure at 67 and 200 μg/g per egg, did not produce individuals with altered testicular weight symmetry, testosterone concentrations, male sexual behavior, or female fecundity.

3.6. Mammals

While there are dozens of studies examining the effects of BPA on mice and rats for extrapolation to human impacts, very little research has tested the impacts of BPA exposure on mammalian wildlife. Specific effects of BPA are difficult to determine in nature, and most mammalian wildlife is likely to experience lower levels of BPA exposure than other taxa. Levels of exposure may vary dramatically depending on the duration of exposure to

contaminated areas, and with water and aquatic food consumption. To our knowledge, the only studies that have examined BPA effects on wild mammals are a study on field voles (*Microtus agrestis*) (Nieminen et al., 2002a) and one on polecats (*Mustela putorius*) (Nieminen et al., 2002b). In field voles but not in polecats, exposure to 250 mg/kg/day resulted in increased testosterone levels.

Assessment of the effects of BPA exposure on mammalian wildlife currently relies on data from laboratory studies on model organisms, which indicate many detrimental effects on rodents at high BPA levels. Such effects include advanced puberty (Howdeshell et al., 1999), increased obesity (Grün and Blumberg, 2009), pregnancy complications (Berger et al., 2008), defects in male and female reproductive organs (Richter et al., 2007), prostate effects, and increases in malignancies (Hunt et al., 2009).

4. Challenges in studying BPA

Endocrine disruptors have challenged toxicological assumptions related to dose–response relationships, differential life-stage effects, and the impacts of chemical mixtures. Toxicity testing has generally involved administering a high dose over a short period, testing evidence of acute effects, and extrapolating a low-dose effect (Vogel, 2004). This method assumes a linear response to increasing and decreasing doses of a toxin, in which substances are generally toxic in large doses, and scientists must determine a level that produces no adverse effect. However, non-linear relationships between dose and response have been observed for some EDCs. For example, an EDC might trigger observable effects at very high and low doses but almost no effect at moderate doses (Calabrese and Baldwin, 2003; Lemos et al., 2009). In such cases, a study evaluating the effects of moderate doses might mistakenly find no low-dose effect. Further, some EDCs may swamp receptors at moderate or very high doses. These chemicals essentially shut down the endocrine system and may be more toxic at low doses (Lister and Van der Kraak, 2001). Such chemicals may necessitate changes to toxicological methods (Borrell, 2010).

Endocrine disruptors can have detrimental effects during specific stages of development and no discernible effect during other life stages. Exposure during early development may have little observable effect until reproductive issues arise later in life. This can make it difficult to establish a cause–effect relationship between currently observed defects and previous exposures, particularly in non-laboratory settings. A study that does not expose specimens to an EDC at these critical windows might demonstrate no adverse effect of exposure (Lister and Van der Kraak, 2001). In addition, the effects of EDC exposure can be subtle and unexpected and therefore can go undetected without highly sensitive tests (Vandenberg et al., 2009; vom Saal and Hughes, 2005). Thus, studies of similar organisms and concentrations of BPA may generate differing conclusions based on the timing of BPA application or the assay utilized to test response.

Laboratory studies generally focus on a single chemical at stable measured doses. In natural systems, wildlife may be exposed to many chemicals at once and the doses may fluctuate. In a recent report, Focazio et al. (2008) found that surface waters of the United States contained a median of four anthropogenic chemicals per testing site, indicating that exposure to chemical mixtures is likely very common. Environmentally relevant mixtures of chemicals may have synergistic or additive effects on wildlife, although these types of mixtures are rarely studied (Hayes et al., 2002).

A final challenge influencing the characterization of wildlife response to BPA exposure relates to toxicological modes of action. Some studies of EDCs use aquatic invertebrates such as cladocerans and copepods as target organisms and report developmental or morphological effects (e.g., Andersen et al., 1999; Marcial et al., 2003). The occurrence of observed effects is not in question; however, it has been suggested that different mechanisms may be operable in invertebrates than in fish and mammals (Hutchinson, 2002). Non-endocrinal modes of action may cause some observed responses (Barata et al., 2004) and differentiating systemic toxicity from endocrine effects poses a challenge to ecotoxicology. One solution to this difficulty may be the development of toxicity thresholds for aquatic organisms analogous to the "maximum tolerated dose" used in mammalian toxicology Hutchinson et al. (2009).

5. Chemical regulation of BPA

Argument exists regarding what concentrations of BPA are dangerous to humans or wildlife, but it is clear that BPA poses potential risks and several countries have considered regulating it. Most proposed regulation addresses human exposure through food contact materials and packaging, but several nations have assessed the risk of environmental exposure to BPA. Although nearly one-third and one-quarter of global BPA production occurs in the US and the European Union, respectively (ICIS, 2008), BPA released into the environment is not strongly regulated in either location (National Institute of Health, 2008). Canada is currently the only country regulating environmental fates of BPA. The following sections review chemical regulation in the US, European Union, and Canada; and describe several important laws that deal with chemicals like BPA in the context of environmental exposures.

5.1. Overview of US chemical policy

Bisphenol A is one of a burgeoning class of chemicals that do not fit well into the current US chemical regulatory structure. Of 87,000 chemicals manufactured or imported into the US, roughly 1000 are regulated under any specific US chemical policy (US Government Accounting Office, 1994). Pharmaceuticals and food additives may be strictly evaluated with regards to their primary intended uses and exposures. However, in the absence of firm evidence of acute toxicity, the hundreds of new chemicals synthesized each year are generally put to use with little regulation and end-of-life issues are rarely addressed (Breggin and Pendergrass, 2007). No US law currently addresses EDCs under a unified and comprehensive framework. When a chemical like BPA reaches the environment via effluent, runoff, or other means, it falls under the jurisdiction of the US EPA, which receives its regulatory authority in part from the Clean Water and the Toxic Substance Control Acts.

5.2. Clean Water Act

The Clean Water Act (CWA) was initially enacted in 1972, with management and enforcement relegated to the US EPA. The first goal of the CWA was to control the most toxic and high-volume industrial point-source polluters in the nation and the second was to trigger badly needed updates in municipal sewage treatment (US Environmental Protection Agency, 1972). At the time of its passing, the CWA legislation was considered ground-breaking and ambitious. The CWA is considered to have been very successful in its primary goals but it has been ineffective in providing a regulatory structure for the hundreds of new chemicals being put into use each year (Andreen, 2003).

When implementing the CWA, the US EPA did not prioritize low-volume or low-toxicity pollutants, although the law allows for such regulation. The wording of the CWA can make adding a chemical to the list of priority pollutants quite cumbersome. For each chemical and type of emitter, this process requires a battery of studies to determine the "best available technology" for chemical

removal and to establish effluent standards (US Environmental Protection Agency, 1972). Given dozens of BPA manufacturers and hundreds of consumer products containing BPA, listing it as a priority pollutant would be a monumental task for the US EPA (US Government Accounting Office, 1994). In the meantime, 700 new chemicals are created for commercial use each year, and the backlog would grow dramatically while the focus is placed on regulating one or two particular chemicals (US Government Accounting Office, 1994). The US EPA has noted this and has effectively decided to place its limited resources toward other, more attainable goals. The list of "priority pollutants" addressed by CWA currently includes 129 chemicals and has not changed, other than the removal of three chemicals, since its drafting in 1977 (US Environmental Protection Agency, 2009a). It is possible that the CWA could be used to regulate BPA discharged into natural systems, but the law might be more effective if it were revised to streamline regulatory processes.

5.3. Toxic Substance Control Act

The Toxic Substance Control Act of 1976 (TSCA) was the first law giving the US EPA authority to regulate chemicals from beginning to end of life (US Environmental Protection Agency, 1976). It was an attempt by lawmakers to strengthen chemical regulations, but in several respects it has been viewed as unsuccessful (Davies, 2007; US Government Accounting Office, 1994). Sections of TSCA that allow the US EPA to gather information about chemicals have been more successful than have sections intended to provide the agency with strong regulatory power (Davies, 2007).

The Toxic Substance Control Act separates chemicals into two main regulatory pools: existing or new chemicals. Manufacturers must submit a Pre-manufacture Notice before utilizing an unregistered chemical (US Environmental Protection Agency, 1976). Manufacturers can voluntarily submit health and safety information on a new chemical, but they are not required to do any independent testing. Computer programs then compare new and existing chemicals to identify similarities to known hazardous substances. If a submitted chemical triggers US EPA concern, the burden of proof shifts to the manufacturer to establish the safety of the chemical (Wagner, 2000); otherwise they move into the TSCA inventory of in-use chemicals (US Environmental Protection Agency, 1976). Since 1976, 21,000 new chemicals have been registered with TSCA, 200 have triggered additional study, and five chemicals have been banned (Vogel, 2004). Once in use, the burden of proof rests on the US EPA to demonstrate detrimental effects of the chemical.

Existing chemicals were essentially grandfathered in under TSCA. This allowed approximately 60,000 chemicals, including BPA, to remain in use with no further testing required at the time of TSCA's enactment (Vogel, 2004). Provisions of the bill that allowed for regulation of existing chemicals were seriously undermined in a 1980 court case when the US Fifth Circuit Court of Appeals overturned the US EPA's ban on asbestos. The agency could not prove either that banning asbestos was the "least burdensome approach" to regulation or that the ban was justified by "unreasonable risk" as phrased within TSCA (Corrosion Proof Fittings vs. EPA, 1991). The court felt that controlling asbestos after environmental release was less burdensome than preventing its use. This precedent left the US EPA unwilling to pursue the regulation of other "existing chemicals" under TSCA (Phillips, 2006; Corrosion Proof Fittings vs. EPA and Reilly, 1991). The references within TSCA to "unreasonable risk" and "least burdensome approach" occur in the portion of the bill that was intended to give US EPA strong regulatory power. A re-wording of these sections might better align the law with its original intent; such an overhaul is widely cited as necessary (Davies, 2007; Wilson and Schwarzman, 2009).

In 2010, the US EPA released a report acknowledging the large amounts of BPA released into the environment (US Food and Drug Administration, 2010). The report states that while there is uncertainty in the interpretation of low-dose effects of BPA, environmental concentrations of BPA may pose some threat to aquatic organisms. The US Food and Drug Administration has also changed its rating of BPA from "generally considered safe" to a chemical of "some concern," indicating that US regulatory agencies are concerned about potential effects of BPA on humans (US Food and Drug Administration, 2010).

5.4. Endocrine Disruptor Screening Program (EDSP)

The US government has been working toward better understanding and eventual regulation of EDCs. In 1996, the US EPA held joint meetings with the World Wildlife Federation and the Chemical Manufacturers Association to discuss EDCs and related research needs (Hotchkiss et al., 2008). Also that year, the Food Quality Protection and Safe Drinking Water Acts mandated that the US EPA develop screening protocols for the impacts of chemicals on endocrine systems and that the agency examine risks posed by mixtures of chemicals, rather than considering substances individually (Hotchkiss et al., 2008). The US EPA responded in part by forming the Endocrine Disruptor Screening and Testing Advisory Committee, which was assigned the task of developing and implementing the Endocrine Disruptor Screening Program (EDSP; Witorsch, 2002). This led to a two-tier process in which chemicals demonstrating hormonal activity must now undergo testing to measure their effects in animals. Although praised as an attempt to provide a consistent framework for screening possible EDCs, the EDSP has two serious weaknesses. First, an estimated 87,000 chemicals could have endocrine effects and adequately assessing all of them would take decades. Second, EDSP provides no authority for eventual regulatory action (Vogel, 2004).

5.5. Overview of chemical regulation in the European Union

The European Union (EU) has a fundamentally different philosophy on chemical regulation based on the REACH (Registration, Evaluation, Authorization and Restriction of Chemicals) policies of 2007. REACH is often considered to be the EU equivalent to TSCA and is intended to manage chemicals of concern to human and environmental health that are manufactured in or imported into the EU (Williams et al., 2009). Chemicals used in food production are managed separately under the jurisdiction of the European Food Safety Authority (EFSA; EFSA, 2010). Before the enactment of REACH, EU chemical regulation policies were akin to those of the US with many of the same characteristics. For example, historical European chemical regulations tended to place the burden of proof on regulatory agencies, had different requirements for new and existing chemicals, and suffered from similarly inefficient regulatory mechanisms (Rogers, 2003; Williams et al., 2009).

The initial structure of REACH was proposed in 2001 (European Commission, 2001) and after years of intense debate, was enacted in 2007 with the goal of phasing in all regulations over a decade (European Commission, 2011). Under REACH, chemical regulations and reporting requirements are different for chemicals produced at higher volumes and for chemicals that are considered dangerous (substance of very high concern or SVHC; Williams et al., 2009). For any chemical imported or produced in quantities greater than 1000 kg per year, REACH requires a thorough registration process. This registration requires the manufacturer or importer to submit specific data on the properties of the chemical. For substances

manufactured or imported in quantities greater than 10,000 kg per year, like BPA, a more intensive chemical safety assessment must be conducted (European Commission, 2011). To date, BPA has not been considered an SVHC under REACH because it has not been shown to be "toxic, carcinogenic, persistent or bioaccumulative" (Plastics Europe, 2012). Chemicals can be considered an SVHC if they are proven to be endocrine disruptors, but BPA did not meet REACH criteria for this classification (Plastics Europe, 2012).

The European Commission conducted a thorough risk assessment of BPA in 2003, and an updated assessment in 2008. Both assessments concluded that at current levels of exposure, BPA is safe for humans and the environment (Plastics Europe, 2012). However, the 2008 risk assessment called for further research on aquatic species (European Union, 2008).

The European Food Safety Authority also conducted extensive risk assessments on the use of BPA as a food contact material. Reports issued in 2007, 2008, and 2010 all concluded that current uses of BPA in food packaging do not pose any substantial risk to humans (European Food Safety Authority, 2010). Dissatisfied with the lack of oversight by REACH and EFSA, several European countries proposed bans on BPA in some products intended for use by infants. France suspended sales of baby bottles containing BPA in 2010 (Bottemiller, 2010). Later that year, the EU banned BPA in baby bottles despite the findings of the EFSA risk assessments (British Broadcasting System, 2010). It is unclear whether these bans on infant products will affect environmental concentrations of BPA or reduce wildlife exposure.

5.6. Overview of regulation in Canada

The Canadian Environmental Protection Act requires regulation of any chemical that may have immediate or long-term deleterious effects on biological diversity or that are found at concentrations that may constitute danger to human health (Environment Canada, 2009). The Canadian government determined that BPA met these criteria, and in 2008–2009 Canada became the first country to take action on BPA by banning its use in baby bottles (Canada Gazette, 2009). In 2008, the Canadian government formally declared BPA to be a hazardous substance and listed BPA among substances considered toxic to human health and the environment (Government of Canada, 2011). In 2010, Canada increased controls on BPA by adding it to Schedule 1 of the Canadian Environmental Protection Act that allows for the development of risk management measures (Canada Gazette, 2010). Also in 2010, new regulations were proposed requiring facilities to develop and implement plans limiting environmental releases of BPA. The new regulatory proposal was based on concerns about the persistence, degradation rates, and release volumes of BPA (Environment Canada, 2010). In a 2009 risk assessment, Canada proposed a limit of 1.75 μg/L for emissions by manufacturers and users of BPA (Environment Canada, 2009). Thus Canada became the first country to consider regulations of BPA specifically intended to reduce the exposure of wildlife and ecosystems.

5.7. Future of BPA regulation

Bisphenol A has several qualities that make it feasible to regulate and manage. The quick breakdown of BPA makes it more amenable to treatment processes than many other chemicals. Studies of water entering and leaving wastewater treatment plants show a 90%–99% reduction in the amount of BPA at the end of the treatment process (Drewes et al., 2005). This indicates that existing technologies might be capable of nearly eliminating BPA from effluents. Also, due to high production volumes, BPA is in a class of chemicals that are prioritized for regulation by both the EU and the US (Burridge, 2003; US Environmental Protection Agency, 2004). Finally, most major sources of BPA into the environment are point source and are thus more easily tracked and regulated (US Environmental Protection Agency, 2004).

Changes may be on the horizon for US chemical regulation policies. A TSCA review and overhaul is planned (US Environmental Protection Agency, 2009b) and the Safe Chemical Act proposed in 2010 had provisions that aimed to give the US EPA authority that was intended by TSCA (Belliveau, 2011). At present it is unclear to what extent TSCA regulations may be improved to cover endocrine disruptors and BPA in particular. Many US manufacturers would prefer a more uniform standard so they could produce a single product for global markets (Wilson and Schwarzman, 2009). Many manufacturers of food containers have already removed BPA from their plastics and because of the notoriety of BPA, these companies and organizations have expressed a desire for official regulation of BPA in food containers (Erickson, 2010).

Many countries that have deemed BPA safe at current levels in past risk assessments are reviewing evidence and updating studies, and several are calling for a new risk assessment from the European Commission (vom Saal and Hughes, 2005). Concerned parties point out that the US assessment of BPA is based on research that is now decades old and that the risk assessment conducted under REACH may have involved conflicts of interest associated with industry-funded research (vom Saal and Hughes, 2005). Japan, another major producer of BPA, is currently reviewing the results of a 2005 risk assessment declaring that the chemical is safe at current levels (Japan National Institute of Advanced Industrial Science and Technology, 2007). The US EPA is considering new regulation and additional testing of BPA, with some action expected in 2012 (US Environmental Protection Agency, 2011). Canada remains the only country that has proposed restrictions on BPA that are not directly related to food contact materials.

6. Remediation

The growing problem of EDC release into the environment requires the development of technologies able to minimize or eliminate adverse environmental exposures (Cabana et al., 2007). Several recently developed methods have been shown to reduce or remove BPA from wastewaters and soils. Ultraviolet irradiation combined with microwaves or heating can breakdown BPA within 90 min and could help to eliminate BPA contamination from point sources (Horikoshi et al., 2004). Further, bioprocesses utilizing enzymes or microorganisms as catalysts for EDC removal have been widely studied and found to be cost effective (Cabana et al., 2007). For example, the enzymatic activity of bioengineered microfibrous mats reduced BPA concentrations by 60% (Ignatova et al., 2009). Microbial degradation pathways can reduce BPA to carbon dioxide and water, or assimilate it into biomass (Kang and Kondo, 2005; Kang et al., 2007; Lobos et al., 1992; Spivack et al., 1994). At least one novel aerobic bacterium (strain MV1) that degrades BPA has been identified (Lobos et al., 1992). These technologies could be used for the removal of BPA from wastewaters and point-source effluents. Additionally, eleven strains of white rot fungi (WRF) have been identified which remove BPA from soils and aqueous solutions. Some WRF strains can remove 100% of BPA-associated estrogenic activity within two hours (Cabana et al., 2007). The benefits of this method include low energy demands, easy system control, and resilience to abiotic variation (Cabana et al., 2007; Saito et al., 2004; Tanaka et al., 2001). Further comparative studies are needed to assess the best applications, and scale of these technologies, as well as cost effectiveness.

7. BPA alternatives

Alternatives to BPA exist; however, there is no one replacement solution for all industrial applications. Brown (2009) noted that switching to alternative chemicals involves trade-offs, and investment in new equipment may be necessary. Potential replacements for BPA-containing polycarbonates include acrylic, polyester, and polypropylene but these materials have drawbacks: acrylic is not as strong and can yellow over time, polyester can be more expensive, and polypropylene is not stable at high temperatures. Alternatives to BPA in can liners include polyester, polyacrylate, synthetic resins, and PVC pastes. Each of these options would have higher costs and may require investment in new equipment by manufacturers. Some of these alternatives also have health effects issues. Still other options exist which have already been in use for decades and are easily recycled, such as glass, stainless steel, and aluminum. Replacement plastics may include high-density polyethylene, polyethylene terephthalate, and Grilamid TR-90. Polyester and oleoresins (plant derived) can also be used as replacement can liners. Tetra paks, constructed from composite paper, polyethylene, and aluminum foil, provide another packaging alternative.

8. Conclusion

Current production of BPA is enormous; the US alone produced over 1 million metric tons in 2007. However, our understanding of BPA-related risks is limited by the challenges BPA presents to traditional toxicological methods. These include non-monotonic dose responses and effects and modes of action that may vary among taxa and life stages. Furthermore, some metabolites of BPA are more estrogenic than the original compound and environmental characteristics may alter degradation rates or biological impacts. In addition, BPA may co-occur with other compounds in mixtures that exert synergistic or additive effects on organisms.

Studies of BPA effects on wildlife have demonstrated few clear trends. Terrestrial wildlife is likely to experience low exposures of BPA, and few studies have examined environmentally relevant doses. However, some invertebrate, fish, and amphibian species appear to be susceptible to low exposures of BPA, and benthic organisms may be exposed to higher concentrations of BPA because of elevated sediment levels. While BPA contamination in the environment is typically at concentrations below 12 μg/L, our examination of the literature has located 11 studies that show measurable effects in wildlife at or near environmentally relevant concentrations (0.08–12.5 μg/L). It is important to note that many wildlife populations are likely affected by environmental BPA concentrations in specific high exposure locations (Crain et al., 2007; Oehlmann et al., 2009). A recent aquatic hazard assessment has lowered the predicted no-effect concentration from 100 μg/L to 0.06 μg/L, which indicates that development, reproduction, and survival of wildlife is likely to be impacted at current environmental ranges (Wright-Walters et al., 2011). As a result, the impact of BPA continues to be a very active area of study, with significant debate regarding low-dose effects (Hotchkiss et al., 2008). Priority areas for additional research include wild population-level effects, vertebrate endocrine-influenced tissue level effects at environmentally relevant concentrations, long-term effects, and the effects of chemical mixtures (Crain et al., 2007; Hayes et al., 2002; Hotchkiss et al., 2008; Oehlmann et al., 2009; Walker et al., 2009).

Although most BPA regulation addresses human exposure through food packaging, these uses account for only a small portion of BPA use. If current trends continue, BPA production and environmental release will increase in the absence of new regulation. A more cohesive framework for regulating EDCs is necessary in the US, and the Endocrine Disruptor Screening Program is a first step in this direction. United States laws such as CWA and TSCA could be utilized to regulate BPA, but weaknesses in the laws have made enforcement difficult. Improved US regulation of BPA would require an overhaul of TSCA, which is widely cited as necessary. Despite an intended comprehensive approach to chemical regulation in the EU, classification criteria and implementation may need to be reassessed based on current research. It is also unclear what effect, if any, recent regulatory changes in the EU and Canada will have on environmental levels of BPA. However, it is important to note that new regulations or a ban on BPA would not necessarily result in a safer or more studied chemical replacement. A more precautionary approach regarding chemical regulation and usage could reduce potential environmental impacts. Issues such as these will continue to arise as humans become increasingly reliant on chemical advances to satisfy global needs.

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