TOXICOLOGICAL PROFILE FOR BISPHENOL A

September 2009

Integrated Risk Assessment Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

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Executive Summary

This toxicological profile on **bisphenol A (BPA)** describes its effects on freshwater and marine life, humans, and laboratory animals. Human exposure to BPA—due to its widespread use, along with reproductive and developmental effects reported in animal studies—has generated considerable attention on this chemical in recent years.

Use and Exposure

BPA is a synthetic chemical, most notably used as a component in the production of:

- Polycarbonate plastic, used in a wide variety of products, including baby and water bottles, sports equipment, medical devices, CDs, and household electronics. These plastics are typically clear and rigid and marked with the number "7" or the letters "PC" near the recycle symbol.
- Epoxy resins, used as coatings to line the inside of food and beverage cans to prevent the contents from reacting with the metal.
- Certain polymers used in dental sealants or composites.

Most human exposures to BPA result from its use in food and beverage containers. BPA can leach into food from containers lined with epoxy resin coatings, and from polycarbonate plastic products. Warming the plastic, such as in a microwave, increases the leaching of BPA into liquids; temperature appears to be a more important factor in leaching than the age of the container

Environmental Occurrence

BPA has been found in lakes, rivers, and the ocean, as well as in sediments and soils. BPA in water bodies is most frequently the result of its presence in municipal wastewater discharges and in leachate from landfills. While most reported levels in fresh water are low, <1 µg/L, some of the higher levels reported in the environment have caused adverse effects in laboratory experiments. No data are available on BPA levels in California marine waters, however, studies conducted around population centers have found BPA at concentrations nearing the Lowest Observed Effect Levels (LOEL). Further research is needed to assess where environmental levels of BPA are likely to cause adverse effects to marine organisms.

Effects on Aquatic Life

Laboratory studies show BPA causes developmental and reproductive effects in aquatic animals, including fish and shellfish. Reproductive and developmental effects reported include:

- Reduction of male hormones in turbot
- Death of testicular cells in swordtails
- Inhibition of spermatogenesis and egg production in fathead minnows, and decreased hatchability of their larvae
- Decreased sperm density and motility in brown trout, along with delayed or absent ovulation
- Fewer eggs and hatchlings in medaka (small experimental fish); embryos were deformed and some had gonads with both male and female elements

- Feminization in both sexes of frogs
- Yolk-sac hemorrhages and edema in Atlantic salmon
- Malformations in tadpoles

A variety of other toxic effects have also been noted.

Health Hazard and Toxicity in Humans and Laboratory Animals

- **Reproductive and Developmental Effects.** The major concern about health effects from exposure to BPA relates to its estrogen-like activity. Estrogens are a group of steroid compounds which function as the primary female sex hormone. Sex hormones influence sexual differentiation, and altered levels of the hormones can have serious effects. Studies in laboratory animals exposed during development (i.e., *in utero* or as immature animals) provide evidence of BPA's effects on the reproductive system, including:

  - Altered mating behavior, maternal behavior, and sex-differentiated emotional and cognitive behavior
  - Enhancement or stimulation of breast growth in female animals
  - Stimulation of prostate growth in male animals

  There is some evidence that BPA has effects on the reproductive ability of adult laboratory animals. Effects on the reproductive system have been observed in adult female and male rodents.

- **Cancer.** No information that BPA causes cancer in humans was found, and there is limited information on its potential to cause cancer in animals. The one long-term animal study reported did not find convincing evidence that BPA caused cancer in rats or mice. However, there are some animal studies to suggest further research is needed.

- **Obesity.** Information of BPA's influence on human obesity is sparse. In animal and cell studies, BPA was found to influence multiple processes related to obesity.

- **Effects on the thyroid.** While evidence from animal and cell studies indicates that BPA can affect the thyroid, conflicting findings have been reported. No information was found for any effects of BPA on the human thyroid.

- **Immune system effects.** BPA has also been shown to affect the immune system of experimental animals, diminishing its ability to mount a protective response against infections.

- **Nervous system effects.** Animal and cell studies show that BPA can affect brain development in areas linked with learning, memory and a variety of behavioral traits. There is concern that BPA might be a factor in the development of human neurological disorders such as attention-deficit/hyperactivity disorder (ADHD) and memory loss, but there is no information on these effects in humans.

Summary Table

This table provides some idea of the availability of information on the toxicology of BPA for the endpoints and organisms identified. It also provides some sense of the evidence available in that information can be used to determine if the endpoint effect does or does not occur. If there is no information the evidence column will be marked with a "--."

Health Effect	Human		Lab Animal		Aquatic Life	
	Information	Evidence	Information	Evidence	Information	Evidence
Reproductive						
male	N	--	S*	S*	Su	Su
female	L	L	S*	S*	Su	Su
Developmental	N	--	Su	Su	Su	Su
Cancer	N	--	S	S	N	--
Immunological	N	--	Su	Su	N	--
Neurological	N	--	Su	Su		
Other Chronic effects					Su	Su
Thyroid	N	--	S	S	L	L
Obesity	L	L	S	S		
Acute					Su	Su

* This information and evidence is for adult animals. Reproductive effects occurring in prenatal and immature animals are considered under Developmental Health Effects.

N = None S = Some
L = Little Su = Sufficient
These rating categories are qualitative in nature and designed to give the reader a general sense of the availability and strength of the information.

Abbreviations

ADHD	attention-deficit hyperactivity disorder
AGD	anogenital distance
ANOVA	analysis of variance
ATP	adenosine triphosphate
ATPase	adenosine triphosphatase
AWQC	ambient water quality criteria
BCF	bioconcentration factor
BMI	body mass index
BPA	bisphenol A (4,4'-dihydroxy-2,2-diphenylpropane
11 β-HSD	β-hydroxysteroid dehydrogenase
cAMP	cyclic adenosine monophosphate
CA1	Cornu Ammonis zone 1
CA3	Cornu Ammonis zone 3
CERHR	Center for the Evaluation of Risks to Human Reproduction
CG	chorionic gonadotropin
ChAT	choline acetyltransferase
CHO	chinese hamster ovary
Con A	concanavalin A
D_n	dopamine-*n* receptor
DART	developmental and reproductive toxicities
DES	diethylstilbestrol
DNA	deoxyribonucleic acid
ECDs	endocrine disrupting chemicals
2-EH	2-ethylhexanol
ER	estrogen receptor
ERL	environmental risk limit
ERR	estrogen related receptor
FSH	follicle-stimulating hormone
GLUT4	insulin-regulated glucose transporter found in adipose tissues
hCG	β-human chorionic gonadotropin
HD	high dose
HPOA	hypothalamic/preoptic area
ICI	ICI 182,780 (Faslodex) from AstraZeneca
IFN	interferon
IgE	immunoglobulin E
IgG	immunoglobulin G
IL	interleukin
iNOS	inducible nitric oxide synthase
KO	knockout
LC_{50}	lethal concentration to 50 percent of the population
LD	low dose
LD_{50}	lethal dose to 50 percent of the population
LH	luteinizing hormone
LOEC	lowest observed concentration

LOELs	lowest observed effect levels
LPS	lipopolysaccharide
LTD	long-term depression
LTP	long-term potentiation
MCP-1	monocyte chemoattractant protein-1
mER	estrogen membrane receptor
MIF	migration inhibitory factor
MIP-1α	macrophage inflammatory protein-1α
µM	micromolar
MPP+	1-methyl-4-phenylpyridinium ion
NADPH	β-nicotinamide adenine dinucleotide phosphate
ncmER	non-classical membrane estrogen receptor
NIS	sodium/iodide symporter
nM	nanomolar
NO	nitric oxide
NOEC	no observed effect concentration
NOELs	no observed effect levels
OEHHA	Office of Environmental Health Hazard Assessment
OPC	California Ocean Protection Council
PCBs	polychlorinated biphenols
p.f.	post-fertilization
PKC	protein kinase C
PND	postnatal day
PPAR-γ	peroxisome proliferators-activated receptor-γ
PPB	parts per billion
PVC	polyvinyl chloride
mRNA	messenger ribonucleic acid
SDN-POA	sexually dimorphic nucleus of the medial preoptic area
SEB	Staphylococcus enterotoxin B
SHBG	sex hormone-binding globulin
SLE	systemic lupus erythematosus
T3	triiodothyronine
T4	thyroxine
THs	thyroid hormones
Th1	T helper cell1
Th2	T helper cell2
TLR	Toll-like receptors
TNF	tumor necrosis factor
TRs	thyroid hormone receptors
TRα	thyroid hormone receptor-α
TRβ	thyroid hormone receptor-β
TSH	thyroid stimulating hormone
VTA	ventral tegmental area
VTG	vitellogenin

Introduction

On February 8, 2007, the California Ocean Protection Council (OPC) passed a resolution, "On Reducing and Preventing Marine Debris." Scientists are investigating whether constituents leach out of plastic products in the marine environment and present a threat to the health of wildlife and humans. The OPC has asked the Office of Environmental Health Hazard Assessment (OEHHA) to prepare toxicity profiles characterizing certain chemical constituents of plastics that may be harmful to marine life and humans. In preparing this profile, OEHHA reviewed reported information on the adverse effects of exposure to BPA in aquatic organisms in the laboratory and in the ambient environment, humans, and experimental laboratory animals.

Properties and Uses

BPA (CAS number 80-05-7) is a synthetic chemical that, because of its structure, has many uses. The bisphenol A (4, 4'-dihydroxy-2, 2-diphenylpropane) (BPA) molecule comprises two phenol rings connected by a methyl bridge, with two methyl groups attached to the bridge (Figure 1).

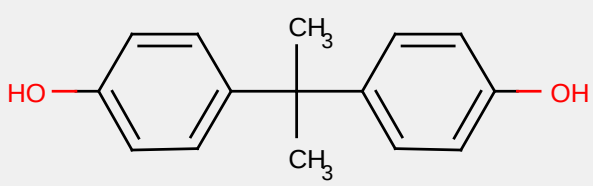

Figure 1: BPA structural formula

Properties of BPA are listed in Table 1.

Table 1: Bisphenol A properties (based on Staples (1998))

PROPERTY	VALUE
Molecular weight	228 gm/mole
Empirical formula	$(CH_3)_2C(C_6H_4OH)_2$
Specific gravity	1.09-1.19 gm/cm^3
Boiling point	398 °C
Melting point	150-155 °C
BCF	5-68
Solubility	120-300 mg/L @ ph7
Log Kow	3.4 (3.3-3.8)
T ½ water & wastewater	2.5-4 days
Vapor pressure	8 E^{-10} – 4 E^{-7} mm Hg
Henry's constant	10^{-10} Atm-m^3/mol
POTW effluent	8-25 µg/L
Bioconcentration factor	5 – 68
Biodegradation	76-95% in 28 days
POTW treatment efficiency	92-99.8%

PROPERTY	VALUE
Effluent seed t ½	3 days
Receiving stream seed t ½	2.5 days
Photodegradation in water	Limited
Photo-oxidation in water	t ½ = 6 -160 days

Most domestically produced BPA is used as an intermediate in the production of polycarbonate and epoxy resins, flame retardants, and other specialty products. Final products include powder paints, adhesives, protective coatings, automotive lenses, protective window glazing, building materials, compact disks, optical lenses, thermal paper, paper coatings, as a developer in dyes, and for encapsulation of electrical and electronic parts. BPA is also used in some polymers used in dental sealants or composites.

Polycarbonate plastic is used to make a variety of common products, including baby and water bottles, sports equipment, and medical devices. These plastics, which are typically clear and rigid, are marked with the recycle symbol "7" or the letters "PC" near the recycle symbol. Epoxy resins are used as coatings to line the inside of almost all food and beverage cans to prevent the contents from reacting with the metal. BPA can migrate into foods from cans and from polycarbonate plastic products such as baby bottles, tableware, and food containers. The use of BPA in food and beverage containers accounts for the majority of daily human exposure; estimated human consumption of BPA from epoxy-lined food cans alone was 6.6 µg/person-day (Howe and Borodinsky, 1998). Warming the plastic, such as in a microwave, increases the leaching of BPA into liquids; temperature appears to be a more important factor in leaching than the age of the container.

Environmental Contamination

The primary route of BPA contamination in the aquatic environment is effluent from wastewater treatment plants and landfill sites (Kang et al., 2007a). Wastewaters from kraft pulp, printing paper, and packing-board paper plants contain high concentration of BPA (Rigol et al., 2004). BPA was also found in wastewater from waste paper recycling plants, which use thermal and printing paper as raw material (Fukazawa et al., 2001; Rigol et al., 2002). Migration from BPA-based products is closely related to BPA contamination of domestic sewage (Kang et al., 2007b; Yamamoto and Yasuhara, 1999). Effluents containing BPA after leachate treatment are a source of BPA contamination in the aquatic environment (Yamamoto et al., 2001). BPA levels in 4 landfill leachates ranged from 15 to 5400 µg/L; after treatment, levels in the effluent ranged from 0.5 to 5.1 µg/L (Yamamoto et al., 2001). Treatment plants were reported to be 37 to 94 percent effective in removing BPA from the waste stream (Fuerhacker, 2003; Kang et al., 2007a). Although BPA levels in river water near wastewater treatment plants or landfills can be high, degradation and dilution result in declining levels with increasing distance from the source (Kim et al., 2004). BPA can migrate from BPA-based products into the aquatic environment and can leach into water from plastic wastes. Yamamoto and Yasuhara (1999) reported that BPA leached from waste plastics, such as polyvinyl chloride (PVC) products and synthetic leather, reaching aqueous concentrations of 1.98–139 µg/L. BPA migration from PVC hoses used for drainage, watering and sprinkling ranged from 4 to 1730 µg/L (Yamamoto et al., 2001). BPA leached into the water from an epoxy-resin tank, reaching a concentration of 7.8 µg/L (Yeo and Kang, 2006).

BPA has been investigated in marine waters in one study. At 28 locations around the Singapore coastline BPA was detected in most samples with a maximum concentration of 2.47 µg/L found at one site while > 70 % of the samples from other locations contained less than 0.4 µg/L (Basheer et al., 2004). The mean maximum concentration is higher than most of those reported from the freshwater locations; however, it is known that BPA persists longer in seawater than in freshwater.

BPA in surface river water can be adsorbed to sediments, based on the Koc values (314–1524) for BPA (Howard, 1989). BPA levels in river water in the United States, Germany, Japan, Spain, China, and the Netherlands, were 21 µg/L or less, while levels in sediment were generally higher than in water, ranging from <0.5 to 1630 µg/kg (Table 2). BPA in anaerobic or semi-aerobic sediment environments can persist for a prolonged period of time. BPA in spiked river samples was greater than 90 percent biodegraded under aerobic conditions, but less than 10 percent decrease in BPA was found under anaerobic conditions after 10 days. Since BPA persists longer in seawater than freshwater, BPA contamination is potentially higher in marine than in freshwater organisms. (Kang et al., 2007a).

Of the 76 Lowest Observed Effect Levels (LOEL) discussed in this report, 11 (14 percent) were 1 µg/L or less and 15 (20 percent) were 5 µg/L or less; this group included effects in mollusks, arthropods, fish, and frogs. Together, these data indicate that environmental BPA concentrations of 5 µg/L or less induce adverse effects in multiple classes of vertebrates and invertebrates. Most of the effects identified at the lowest environmental concentrations are reproductive or developmental effects.

Crain et al (2007) reviewed the environmental concentrations and possible environmental effects of BPA. They concluded that most measured concentrations in the environment are below levels associated with adverse effects on aquatic organisms. However, occasionally environmental concentrations as high as 25 µg/L have been measured, particularly near point sources such as outfalls from pulp mills, sewage treatment plants, or landfills. These levels exceed the lowest effect concentrations in aquatic organisms (Appendix 1) and thus could potentially cause some adverse effects on aquatic ecosystems.

Crain et al (2007) summarize these data graphically, showing measured environmental concentrations and reported chronic values (geometric mean of LOEL and No Observed Effect Levels (NOEL)) on the same axes, with concentration as the ordinate and chronic values as the abscissa. This presentation shows that 80% of the measured environmental concentrations exceed the lowest reported chronic value, and that about 30% of the measured environmental concentrations exceed the 20^{th} percentile chronic value. This supports the conclusion that some of the more sensitive species could be affected at upper-end environmental concentrations of BPA. Unfortunately, most of the environmental concentration data are from fresh water systems. It would be useful to gather data on BPA prevalence in marine environments, especially near municipal and industrial outfalls, landfills, and other possible point sources of BPA.

Table 2: BPA levels in water and sediment

Water (µg/L)	Sediment (µg/kg)	Country	References *
0.0005 – 0.014	no data	Germany	(Kuch and Ballschmiter, 2001)
0.0005 – 0.41	10 - 190	Germany	(Fromme et al., 2002)
<0.001	2.1	Venice lagoon	(Pojana et al., 2007)
<0.001	60	Venice lagoon	(Pojana et al., 2007)
0.0035	118	Venice lagoon	(Pojana et al., 2007)
0.0035	25	Venice lagoon	(Pojana et al., 2007)
<0.002 – 2.47	no data	Singapore	(Basheer et al., 2004)
0.004 – 0.092	10 - 380	Germany	(Stachel et al., 2003)
<0.005 – 0.08	<0.5 - 13	Japan	(Kawahata 2004)
<0.0088 – 1	<1.1 - 43	Netherlands	(Vethaak et al., 2005)
0.009 – 0.776	66 - 343	Germany	(Heemken et al., 2001)
0.01 – 1.4	no data	Japan	(JMC, 1999)
0.01 – 1.9	no data	Japan rivers	(Staples et al., 1998)
<0.012 – 21	no data	Netherlands	(Belfroid et al., 2002)
0.02 – 0.03	0.11 - 48	Japan	(Hashimoto et al., 2005)
0.02 – 0.15	no data	Japan	(Takahashi et al., 2003)
0.03 – 0.083	no data	China	(Jin et al., 2004)
<0.05 – 0.272	<0.5 - 15	Germany	(Bolz et al., 2001)
<0.05 – 1.51	no data	Spain	(Cespedes et al., 2006)
<0.09	no data	Japan	(Matsumoto et al., 1977)
≤0.119	no data	Rhine River	(Staples et al., 1998)
<0.2 – 1.9	no data	Japan	(Matsumoto, 1982)
<0.5 – 0.9	no data	Japan	(Kang and Kondo, 2006)
<1 – 8	no data	United States	(Staples et al., 2000)
8 – 25	no data	US POTW effluent	(Staples et al., 1998)
no data	<5 - 1630	Germany	(Stachel et al., 2005)
no data	0.6 - 3.8	China	(Peng, 2006)
no data	204	Osan Bay, Korea	(Koh et al., 2002)

* underlined references are secondary references cited in (Kang et al., 2007a)

Environmental Fate, Transport, and Bio-uptake

This section describes what happens to BPA when it enters aquatic environments. Table 3 summarizes the environmental and bio-uptake data. McKay level 1 modeling, which estimates the distribution of a contaminant in different environmental compartments, predicted about 25 percent of an environmental release of BPA would be found in soil, 25 percent in sediment and 50 percent in water with less than 1 percent in biota (Staples et al., 1998). Plants can rapidly absorb BPA through their roots from water and metabolize it to several glycosidic compounds. Glycosylation, the main route of BPA metabolism in plants, leads to loss of estrogenicity of the parent compound. BPA mono- and di-b-D-glucopyranosides show reduced or no estrogenic activity in in vitro tests (Morohoshi et al., 2003). Two oxidative enzymes, peroxidase and polyphenol oxidase, are associated with BPA metabolism (Kang et al., 2007a; Kang et al., 2006).

Photolysis and photo-oxidation are the main non-biological pathways of BPA breakdown in the aquatic environment. Photodegradation of BPA is slow in pure water, but can be accelerated in the presence of: a) dissolved organic matter, including humic and fulvic acid (Chin, 2004; Peng, 2006; Zhan, 2006), b) reactive oxygen species, including hydroxyl radicals, peroxyl radicals and singlet oxygen (Sajiki, 2002; Sajiki, 2003; Zhan, 2006), and/or c) ions, including ferric and nitrate ions (Peng, 2006; Zhan, 2006; Zhou, 2004). In artificial indoor streams, DT_{50} values (time when 50% of initial BPA disappeared) were about 1 day (Licht et al., 2004)

BPA has been found in a number of market seafood species. In Singapore, Basheer et al. (2004) found 13.3 – 213.1 µg/kg ww of BPA in prawn, crab, blood cockle, white clam, squid, and fish purchased from local supermarkets, indicating the potential for human exposure by eating contaminated seafood.

Zebrafish initially eliminated parent BPA with a hafe-life of 1.1 hours; a second phase had a half-life of 39 hours (Lindholst et al., 2003). Metabolites included sulfate and glucuronic acid conjugates.

The bacterium Pseudomonas paucimobilis FJ-4 rapidly biodegraded BPA to less toxic metabolites. The parent compound was undetectable by 12 hours of incubation. Total organic carbon was reduced by 85 percent within 48 hours (Ike et al., 2002).

Table 3: Bio-uptake and Bioconcentration

Organism or Tissue	**Water (µg/L)**	**Tissue (µg/kg)**	**Bioconcentration Factor**	**Reference***
Periphyton	0.02 - 0.15	2-8.8	18-650	(Takahashi et al., 2003)
Benthos	0.02 - 0.15	0.3-12	8-170	(Takahashi et al., 2003)
Fish liver	<0.01 – 0.33	2 – 75 (DW)		(Belfroid et al., 2002)
Fish muscle	<0.1 – 0.33	1 – 11 (DW)		(Belfroid et al., 2002)
fish	<.18	1-6 (DW)		(Belfroid et al., 2002)
Rainbow trout (*Oncorhynchus mykiss*)			5-68	(Lindholst et al., 2000) (Staples et al., 1998)
Rainbow trout (*Oncorhyncus mykiss*)	100	271-357	2.7 – 3.6	(Lindholst et al., 2003)
Zebrafish (*Danio rerio*)	100	569	5.7	
FW clam (*Pisidium amnicum*)			110-144	(Heinonen et al., 2002)
Salmon (*Salmo salar*) fry			94-182	(Honkanen et al., 2004)
Prawn (*Penaeus monodon*)	<0.002 – 2.47	13		(Basheer et al., 2004)
Crab (*Portunus*	<0.002 – 2.47	213		(Basheer et al., 2004)

Organism or Tissue	Water (µg/L)	Tissue (µg/kg)	Bioconcentration Factor	Reference*
pelagicus)				
Blood cockle (*Anadara granosa*)	<0.002 – 2.47	57		(Basheer et al., 2004)
White clam (*Meretrix meretrix*)	<0.002 – 2.47	27		(Basheer et al., 2004)
Squid (*Loligo* sp.)	<0.002 – 2.47	119		(Basheer et al., 2004)
Indian scad fish (*Decapterus russelli*)	<0.002 – 2.47	66		(Basheer et al., 2004)
Frog (*Rana temporaria*)	1.8	250	140-164	(Koponen et al., 2007)

* (underlined references are secondary references cited in (Kang et al., 2007a)

Toxicology: Marine and Other Aquatic Organisms

Reproductive and Endocrine Toxicity

As noted in the summary table, there is sufficient qualitative information on reproductive and developmental toxicity of BPA to aquatic organisms. Crain et al. (2007) reviewed the environmental toxicology of Bisphenol A (BPA), concluding that BPA can disrupt the endocrine system of a variety of species at environmentally relevant concentrations of 21 µg/L or less. Reported male reproductive effects include: apotosis of testicular cells in swordtail freshwater fish (Kwak et al., 2001), inhibition of gonadal growth and spermatogenesis in fathead minnows (Sohoni et al., 2001), decreased sperm density & motility in brown trout (Lahnsteiner et al., 2005), reduction of testosterone and 11-ketotestosterone in turbot (Labadie and Budzinski, 2006), and induction of an intersex condition known as "testis–ova" in medaka (Metcalfe et al., 2001). Exposure levels for these studies are reported in Appendix 1. Additionally, when male medaka were exposed to 10 µmol/L BPA and placed with fertile females, reduced number of eggs and hatchlings were observed; no significant decreases were observed at BPA concentrations of 0.3, 1 and 3 µmol/L (Shioda and Wakabayashi, 2000)..

Reported female reproductive effects include: inhibition of gonadal growth and egg production in fathead minnows (Sohoni et al., 2001), decreased hatchability of in flathead minnow larvae (Sohoni et al., 2001), delay in, or complete cessation of ovulation in brown trout (Lahnsteiner et al., 2005), reduced number of eggs and hatchlings in medaka (Shioda and Wakabayashi, 2000), induction of Atlantic salmon eggshell zona radiata protein (Arukwe et al., 2000), and increased choriogenin mRNA expression in medaka (Tyl et al., 2002). Choriogenin is a precursor to the formation of the protein subunits of the zona radiata. BPA exposure at 59 µg/L for 3 weeks led to an elevation of estrone level in turbot (Labadie and Budzinski, 2006). High concentrations of BPA may have both morphological and histological effects on salmon yolk-sac fry; at three concentrations (10, 100 and 1000 µg/L) changes in behaviour, morphology and histological structure were observed including fluid accumulation (oedema) in the yolk sac and haemorrhages

in the front part of the yolk sac and in the head around the gill arches at 1000 µg/L (Honkanen et al., 2004). Perturbations in markers of early development also have been observed in zebrafish (Kishida et al., 2001), and embryo lesions and deformities have been observed in medeka at 200 µg/L (Pastva et al., 2001). Effects on the offspring include embryo lesions and deformities at 200 µg/L, and yolk-sac hemorrhages and edema at 1000 µg/L (Honkanen et al., 2004 ; Kishida et al., 2001; Pastva et al., 2001).

The vitellogenin (VTG) assay is a frequently used *in vivo* biomarker for estrogenicity in oviparous vertebrates (Heppell et al., 1995; Lattier et al., 2001). BPA induces synthesis of VTG and other proteins in multiple species at concentrations ranging from 59 to 2000 µg/L (Arukwe et al., 2000 ; Brian et al., 2005; Kang et al., 2002 ; Kashiwada et al., 2002 ; Kwak et al., 2001; Lindholst et al., 2000 ; Rankouhi et al., 2004; Sohoni et al., 2001 ; Tabata et al., 2004 ; Van den Belt et al., 2003). VTG is a large (molecular mass 250–600 kD), complex, calcium-binding phospholipoglycoprotein required for normal oocyte maturation in developing females (Matozzo et al., 2007). It is produced in the liver in response to estrogen stimulation, secreted in the blood, and transported to the oocyte, where it is incorporated as constituents of the yolk. Being estrogen-dependent, VTG production is normally restricted to females; little if any VTG can be detected in males or sexually immature females. However, males do carry the VTG gene and exposure to estrogens can trigger its expression (Sumpter and Jobling, 1995). VTG can be measured in the liver, blood, and mucus from male and female fish as well as in primary hepatocyte cultures (Navas and Segner, 2006).

BPA at concentrations as low as 0.01 µmol/L for 120 days has caused feminization in tadpoles of both sexes of clawed frogs (*Xenopus laevis*) (Kloas et al., 1999; Levy et al., 2004). Liver vitellogenin mRNA was induced in male frogs (*Bombina orientalis*) (Gye and Kim, 2005). Complete sex reversal has been observed in caimen exposed to 140 mg/L BPA which is within the solubility of BPA but higher than any levels reported in the environment (Stoker et al., 2003).

Gonadal resorption has been reported in mussels exposed to 50 µg/L BPA for 3 weeks (Cajaraville and Ortiz-Zarragoitia, 2006; Ortiz-Zarragoitia and Cajaraville, 2006). In male freshwater snails (*Marisa cornuarietis*) and in marine dogwhelks (*Nucella lapillus*), BPA at concentrations ranging from 1 to 100 µg /L for 5 months has caused reductions in the size of the penis and prostate and decreased mature sperm in the vesicula seminalis (Oehlmann et al., 2000). In female Marisa snails, enlarged accessory pallial sex glands, increased oocyte production, superfemales, and oviduct malformations have been reported at concentrations as low as 1 µg BPA/L (Oehlmann et al., 2006; Oehlmann et al., 2000). Superfemales are characterized by the formation of additional female organs, enlarged accessory sex glands, gross malformations of the pallial oviduct, and a stimulation of egg and clutch production, resulting in increased female mortality. Conversely, no differences in the number of eggs per female per month, the percentage of eggs hatching successfully, or difference in time to hatching between unexposed *Marisa* snails and snails exposed to concentrations of 0.1, 1, 25, and 640 µg/L for six months were found (Forbes et al., 2008). In mudsnails (*Potamopyrgus antipodarum*), induction of unshelled embryos and embryo production have been reported when exposed to 30 – 300 µg/kg dw in sediment (Duft et al., 2003; Jobling et al., 2003; Jobling and Tyler, 2003).

BPA concentrations of 20 µg/L for 10 days induced maturation of reproductive organs and egg production in female copepods, small crustaceans found in marine and freshwater habitats. Similar effects were seen at concentrations of 2 and 0.2 µg/L, but they were not statistically significant at these levels (Andersen et al., 1999). Long-term exposure of the copepod *Tigriopus*

japonicus to 0.1, 1.0 and 10 µg/L BPA caused a significant delay in completion of the naupliar stages compared to the controls in the parental generation, and at 0.01 µg/L and above in the F_1 generation (Marcial and Snell, as reviewed by (Crain et al., 2007)). BPA concentrations as low as 0.08 µg/L delayed emergence of F_2 male and female midges *Chironomus riparius* (Watts et al., 2001a). At 10,400 µg/L BPA, it completely inhibited egg hatching and emergence of the F_2 generation. The sperm and eggs of sea urchins (*Paracentrotus lividus)* were exposed to BPA concentrations of 300–3500 µg/L under static conditions. The 300 µg/L BPA concentration resulted in reduced fertilization, reduced growth, and an increased number of larvae with skeletal malformations while a significant decreased percentage of fertilized eggs was not observed until greater than 1000 µg/L; results of the study indicate that that the BPA has less effects on fertilization success of sperms while the decreased offspring quality of exposed sperms is more important from the ecotoxicological point of view. (Ozlem and Hatice, 2008). In freshwater sponges, (Hill et al., 2002) reported abnormal growth at 16,000 µg/L BPA for 6 days, and at even higher concentrations, complete inhibition of germination. Fukuhori et al. (2005) reported suppression of testis formation and sexual reproduction and induction of asexual reproduction in hydra when exposed to 500–3000 µg/L BPA for 35 days. However, the concentrations used in these experiments are not likely to be environmentally relevant.

Other Toxic Effects

As noted in the summary table, there is sufficient qualitative information on acute and chronic toxicity of BPA to aquatic organisms. There is no information on immunotoxicity or carcinogenisis. BPA can reduce survival and growth in teleost (bony) fish (Kishida and Callard, 2001; Sohoni et al., 2001; Yeo and Kang, 2006). In goldfish it reduces calcitonin secretion and plasma calcium levels, while suppressing tartrate-resistant acid phosphatase and alkaline phosphatase b (Suzuki and Hattori, 2003; Suzuki et al., 2003a). Other findings include stained fragments in hepatocyte nuclei and chromosomal damage in erythrocytes (Bolognesi et al., 2006; Honkanen et al., 2004).

In *Xenopus laevis* larvae, 10-25 µmol/L BPA for 21 days suppressed thyroxin receptor β gene expression. This may explain the suppressed spontaneous and thyroxin-induced metamorphosis. Other findings in *Xenopus laevis* embryos and tadpoles include malformation and apoptosis of central nervous system cells, scoliosis, short body length, flexure, edema, and abnormal gut coiling, microcephaly and other malformations of the head, and up to 75 percent mortality (Iwamuro et al., 2003; Oka et al., 2003). Similarly, BPA reduced expression of preprotemporin-1TGb and 1Tga genes, resulting in inhibition of thyroid hormone activity, induction of thyroxine, developmental malformations, and up to 90 percent mortality in *Rana sp.* tadpoles (Koponen et al., 2007; Ohnuma et al., 2006; Yang et al., 2005).

In the mussel, *Mytilus galloprovincialis*, BPA (25 nM nominal concentration in the hemolymph) lead to a significant lysosomal membrane destabilization (LMS), indicating BPA-induced stress conditions in the hemocytes, whereas lower concentrations were ineffective (Canesi et al., 2005). The NOEC for BPA in terms of LMS was 1 µM and the LOEC was 5 µM (Canesi et al., 2007). BPA also induced significant changes in the phosphorylation state of MAPK and STAT members, indicating that BPA can affect kinase-mediated cell signaling (Canesi et al., 2005) and decreased serine phosphorylation of a CREB-like protein in mussel hemocytes (Canesi et al., 2005); CREB isoforms have been identified in invertebrates in relation to its role in neuronal plasticity and learning. At the organismal level, BPA inhibited regeneration in isolated digestive regions in hydra at relatively high concentrations (> 460 µg/L) (Pascoe et al., 2002) and in

chironomids caused mouthpart deformities at as little as 0.01 µg/L and reduced weight and delayed molting at 1000 µg/L (Watts et al., 2003).

Summary and Aquatic Hazard Assessment

Toxic effects of BPA in aquatic organisms are summarized in Appendix 1. Most of these studies are short-term laboratory studies involving a single species. Experiments conducted with environmentally relevant concentrations of BPA resulted in observed effects in medaka, brown trout, zebrafish, mollusks, and copepods. BPA induces endocrine manifestations, malformations, changes in growth, chromosomal damage, biochemical changes and, at sufficiently high concentrations, mortality. Most of the effects identified at the lowest environmental concentrations are reproductive or developmental effects; there are adequate data to support the conclusion that BPA is a reproductive toxicant in the aquatic environment. The potential for adverse effects at lower aqueous concentrations when the exposure is longer-term and/or via the food web remain largely unexplored. Adverse effects in benthic organisms have not been well studied. Benthic (sediment-dwelling) organisms are likely to receive much higher exposures, since BPA concentrations are higher in sediment than in the water column.

Human and Laboratory Studies

Reproductive and Developmental Effects

Introduction

Endocrine disruptors cause adverse health effects in humans and wildlife subsequent to changes in endocrine function. BPA is among the chemicals identified as a potential endocrine disruptor based on its estrogenic properties. Studies in laboratory animals have focused on understanding the consequences of BPA for estrogenic activity, taking into account the variety of estrogen receptors (ER) and estrogen binding molecules and their functions in different reproductive processes and different stages of the life cycle. Estrogen has a pervasive effect on body function in both males and females through a variety of mechanisms. The action of BPA at ERα, ERß, estrogen related receptor (ERR), and the estrogen membrane receptor (mER) has been documented (Wetherill et al., 2007). Epigenetic effects of BPA have also been demonstrated (Dolinoy et al., 2007; Prins et al., 2008). Further, the estrogen receptor belongs to a large family of gene products, the nuclear steroid hormone receptor superfamily, which have some ligand cross reactivity. This family of nuclear receptors is present in all known vertebrates (Thornton, 2001). For example, both estrogen and BPA bind to the thyroid receptor and antagonize the androgen receptor (Wetherill et al., 2007).

Some consideration should be given to the relevance of the findings in laboratory animals (mostly mice and rats) to marine life. As an estrogenic agent, BPA is thought to act through the estrogen receptor (ER). Invertebrates have a variant ER (based on DNA sequencing), which does not however, bind estrogen. Simpler animals, including the metazoan trichoplax have DNA coding for a protein similar to ER, termed the estrogen related receptor (ERR), which also does not bind estrogen (Baker, 2008). BPA binding to the invertebrate ER and the ERR has not been determined. Information on evolution and DNA sequencing cannot provide specific predictions about BPA toxicity in marine life based on rodent toxicology. Perhaps a more reliable source of prediction is the general concordance between reproductive toxicity of chemicals in humans and

wildlife as discussed in the endocrine disruption literature (Colborn, 1994; Hotchkiss et al., 2008).

Laboratory Rodent Studies

Laboratory mice and rats are the most commonly used biomedical rodent models for studying potential BPA human health effects. Three issues have emerged as important in interpreting this literature: (1) mouse and rat strains differ in their sensitivity to various effects of estrogenic agents; (2) severity of effect does not always increase with dose and qualitative differences emerge along the dose-response continuum; (3) the laboratory environment may contain other estrogenic agents (in feed, water, caging and bedding) that need to be taken into account. A major discussion in the literature and regulatory programs centers around the occurrence of BPA effects at doses < 5 mg/kg/d (low dose effects) which are not seen at greater severity/incidence at higher doses (National Toxicology Program, 2001). More commonly, toxic effects seen at low doses persist and are magnified at higher doses. Scientific information relevant to this discussion continues to develop. Thus, extrapolation of the animal studies to the effects of human exposures, or exposures in the aquatic environment, requires careful review of this extensive literature as well as continuing update of the database.

A number of hypotheses have been generated and tested, and a literature with more than1200 articles has accumulated primarily over the past 10 years. Effects that have been identified in some laboratory animal models and subsequently studied in greater depth are outlined in Table 4. These studies have been summarized by a panel of scientists active in this research area (Richter et al., 2007a) as well as by private and governmental agencies (CERHR, 2007; Health Canada, 2008; Willhite et al., 2008). This overview of the literature relied in part on these summaries.

Table 4. Developmental and reproductive endpoints affected by BPA. A brief description of the types of effect seen in studies which found BPA effects is provided. Studies that examined the endpoint but did not find BPA effects are also cited. These studies do not necessarily contradict the studies with findings due to differences in size and conduct of the studies.

Endpoint	Models*	Effect	Citation
Genital differentiation; anogenital distance	Mice, rats, developmental oral, injection	Increase, decrease or no effect	(Ema et al., 2001; Gross, 2007; Gupta, 2000; Honma et al., 2002; Howdeshell et al., 2008; Kobayashi et al., 2003; Kobayashi et al., 2002b; Takagi et al., 2004; Tinwell et al., 2002; Tyl et al., 2008; Tyl et al., 2002)
Prostate gland development	Mice, rats developmental, adult, Oral, injection	Increased adult prostate size and altered gene expression	(Ashby et al., 1999; Cagen et al., 1999a; Cagen et al., 1999b; Chitra et al., 2003a; Elswick et al., 2000; Gupta, 2000; Herath et al., 2004; Ho et al., 2006; Nagao et al., 2002; Nagel et al., 1997; Nishino et al., 2004; Ramos et al., 2003; Ramos et al., 2001; Richter et al., 2007b; Takahashi and Oishi, 2003; Talsness and Chahoud, 2000; Timms et al., 2005; Welshons et al., 1999; Yoshino et al., 2002)
Mammary gland	Mice, rats, developmental, gavage, injection, minipump	Enhanced growth and differentiation	(Colerangle and Roy, 1997; Durando et al., 2007; Markey et al., 2001; Moral et al., 2008; Muñoz-de-Toro et al., 2005; Murray et al., 2007; Nikaido et al., 2004; Vandenberg et al., 2007)
Spermatogenesis	Mice, rats, developmental, adult, oral, injection	Reduced sperm number, morphology, motility	(Aikawa et al., 2004; Al-Hiyasat et al., 2002; Ashby et al., 2003; Chitra et al., 2003a; Chitra et al., 2003b; Ema et al., 2001; Herath et al., 2004; Howdeshell et al., 2008; Kato et al., 2006; Sakaue et al., 2001; Takahashi and Oishi, 2001; Takahashi and Oishi, 2003; Tinwell et al., 2002; Toyama et al., 2004; Toyama and Yuasa, 2004; Tyl et al., 2008; Yoshino et al., 2002)
Reproductive hormones	Mice, rats, developmental, oral, injection	Lower testosterone	(Akingbemi et al., 2004; Della Seta et al., 2006; Kawai et al., 2003; Kobayashi et al., 2002a; Saito et al., 2003; Takao et al., 1999; Tanaka et al., 2006; Tanaka et al., 2001; Watanabe et al., 2003)

Endpoint	Models*	Effect	Citation
Estrous cycling	Mice, rats, developmental, oral injection, minipump	Disrupted/delayed estrous cycles	(Ema et al., 2001; Kato et al., 2003; Nikaido et al., 2005; Nikaido et al., 2004; Rubin et al., 2006; Ryan and Vandenbergh, 2006; Tyl et al., 2008; Tyl et al., 2002)
Reproductive behavior	Mice, rats, developmental, adult, oral	Fewer mating behaviors	(Farabollini et al., 2002; Funabashi et al., 2003; Ryan and Vandenbergh, 2006; Welsch et al., 2000)
		Less maternal behavior	(Della Seta et al., 2005; Palanza et al., 2002)
Aggression	Mice, rats, developmental, oral, injection	More aggression	(Farabollini et al., 2002; Kawai et al., 2003; Patisaul and Bateman, 2008; Patisaul et al., 2006)
Sex-differentiation of the brain and behavior	Rats, developmental, oral, injection	Less sex differentiation	(Aloisi et al., 2002; Carr et al., 2003; Fujimoto et al., 2006; Kubo et al., 2001; Kubo et al., 2003; Kwon et al., 2000; Patisaul and Bateman, 2008; Patisaul et al., 2006; Patisaul et al., 2007)
Growth and growth regulation	Mice, rats, developmental, oral, minipump, in vitro	Acceleration of growth	(Howdeshell et al., 1999; Howdeshell and vom Saal, 2000; Miyawaki et al., 2007; Morrissey et al., 1989; Rubin et al., 2001; Takai et al., 2001)
Puberty onset	Mice, rats, developmental, oral, injection	Early in females, late in males	(Durando et al., 2007; Honma et al., 2002; Howdeshell et al., 2006; Howdeshell and vom Saal, 2000; Kato et al., 2003; Nikaido et al., 2004; Ryan and Vandenbergh, 2006; Tinwell et al., 2002; Tyl et al., 2008; Tyl et al., 2002)

* species, time of exposure (developmental, adult), route of exposure

As is the case for aquatic organisms (see section on "Reproductive and Endocrine Toxicity" under "Toxicology: Marine and Other Aquatic Organisms"), sexual differentiation has been a major topic of research in laboratory animals. After the period of organogenesis, sexual differentiation of the brain and the reproductive tract occurs in many birds and mammals under the influence of the hormones produced in the gonads (ovaries or testes). Exogenous hormones and synthetic chemicals that interact with the endocrine system are known to alter this process (Wilson et al., 2007). In the brain, sexual differentiation in terms of size, cell number and expression of relevant neurotransmitters and hormone releasing factors has been shown to be affected by developmental exposure to BPA. Externally, the genitalia differentiate in terms of anogenital distance, testes descent, and later vaginal opening and preputial separation at puberty. While no studies have shown that BPA can completely transform morphological gender identity,

mating behavior, maternal behavior and sex-differentiated emotional and cognitive behavior are endpoints influenced by developmental BPA exposure. In addition, quantitative changes in morphological indices like anogenital distance have been demonstrated. Finally, timing of puberty, as reflected in morphological markers such as vaginal opening in females, has been reported to be affected by BPA.

Of particular interest has been the development of the prostate and mammary glands, secretory organs of the reproductive system. The prostate produces and excretes a portion of the seminal fluid while the mammary gland produces milk during lactation. Both structures grow and differentiate under the influence of gonadal hormones fully maturing around the time of puberty. The effect of BPA on mammary glands can be characterized as enhanced development relative to same age controls and has been demonstrated after in utero exposures. In the prostate gland, development is also stimulated by in utero BPA in terms of prostate weight as well as duct structure.

In addition to an emphasis in the scientific literature on reproductive tract development, studies screening for general effects on fertility and pregnancy outcome have been conducted using government guidelines (FIFRA FDA). Developmental toxicity studies (examining term fetuses after exposure during organogenesis) are rare (Hardin et al., 1981; Kim et al., 2001; Morrissey et al., 1987) but did not report an increased incidence of skeletal malformations. There are also multigeneration studies in which parents and offspring are continually dosed over several generations (Ema et al., 2001; Tyl et al., 2008; Tyl et al., 2002). These studies have not reported effects on fertility. Using another study design (continuous breeding) in mice, fertility was not affected but fewer litters were seen with BPA treatment (Morrissey et al., 1989). Effects on implantation, resorption and intrauterine growth retardation (Hardin et al., 1981; Morrissey et al., 1987; Morrissey et al., 1989) were reported at the higher doses levels. Other studies have also reported effects on implantation and resorption (Al-Hiyasat et al., 2002; Berger et al., 2007). Postnatal growth retardation was also observed in the multigeneration studies as well as in hypothesis testing studies (Matsumoto et al., 2004; Negishi et al., 2003b; Takagi et al., 2004). Growth retardation is a sensitive index of disruption of reproductive and developmental processes. Adult female laboratory rodents exposed to BPA, via injection and oral routes, also show some reproductive system alterations (Table 5a). Commonly reported effects of BPA on the adult female reproductive system include an increase in uterine weight, and changes in uterine and vaginal epithelium, changes that are often used as indices of estrogenic action.

Table 5a: Effects of subchronic/chronic exposure of adults to BPA on female reproductive parameters

Endpoint	Model	Effect	Citations
Uterus	Swiss mice, Alpk:APfSD (Wistar derived) rats, Crj:CD(SD) rats, Long Evans rats, Sprague-Dawley rats	↑ uterine weight	(Al-Hiyasat et al., 2004; Ashby et al., 2000; Ashby and Tinwell, 1998; Dodge et al., 1996; Freyberger et al., 2002; Yamasaki et al., 2000)
		Hypertrophy of epithelial, stromal, and myometrial cells	(Freyberger et al., 2002)

Endpoint	Model	Effect	Citations
		Uterotrophic response	(Laws et al., 2000)
Vagina	Alpk:APfSD (Wistar derived) rats, Long Evans rats	Hypertrophic cells	(Freyberger et al., 2002)
		↑ % vaginal cornified cells	(Ashby et al., 2000)
		No change in cytology	(Laws et al., 2000)
Estrous Cyclicity	Crj:CD (SD) IGs rats, Sprague-Dawley rats	No changes in F_0 generation	(Ema et al., 2001; Tyl et al., 2002)
Fertility	Crj:CD (SD) IGs rats, Sprague-Dawley rats	No changes in F_0 generation	(Ema et al., 2001; Tyl et al., 2002)
Mating	Sprague-Dawley rats	No changes in F_0 generation	(Tyl et al., 2002)
Pregnancy	Swiss mice, Sprague-Dawley rats	↑ in total # of resorptions	(Al-Hiyasat et al., 2004)
		No changes in F_0 generation	(Tyl et al., 2002)
Gestation Length	Sprague-Dawley rats	No changes in F_0 generation	(Tyl et al., 2002)
Estrogen Receptor	Pregnant/lactating or estrous cycling rats	↓ ER-immunoreactive cells in the brain of lactating females compared with non-lactating	(Aloisi et al., 2001)

Like female laboratory rodents, adult male laboratory rats and mice exposed to BPA show alterations in their reproductive system. Commonly examined endpoints include the testes, epididymis, prostate, and seminal vesicle (Table 5b).

Table 5b: Effects of subchronic/ chronic exposure of adults to BPA on male reproductive parameters

Endpoint	Model	Effect	Citation
Testis	Wistar rats, Sprague-Dawley rats, Crj: CD-1 mice; Swiss mice	↓ testis weight	(Al-Hiyasat et al., 2002; Chitra et al., 2003b; Takahashi and Oishi, 2001)
		No histological alterations	(Sakaue et al., 2001)
		↑ testis weight	(Takahashi and Oishi, 2001)
		No change in weight	(Ashby et al., 2003; Tyl et al., 2002)
Epididymis	Crj: CD-1 mice, Wistar rats, Sprague-Dawley	↓ epididymal weight	(Chitra et al., 2003b; Takahashi and Oishi, 2001)
		No change in weight	(Ashby et al., 2003; Tyl et al., 2002)
Prostate	Sprague-Dawley	No change in weight	(Ashby et al., 2003)
Seminal Vesicle	Sprague-Dawley;	No change in weight	(Ashby et al., 2003)

Endpoint	Model	Effect	Citation
	Swiss mice	↓ in weight	(Al-Hiyasat et al., 2002)
Sperm / Spermatogenesis	Sprague-Dawley rats; Crj:CD(SD) IGS rats; Swiss mice; ICR mice; Wistar rats, CD-1 mice	No changes in daily sperm production	(Ashby et al., 2003; Sakaue et al., 2001)
		No effect on sperm [concentration, motility, production, morphology]	(Ema et al., 2001; Tyl et al., 2002)
		↓ testicular and epididymal sperm counts	(Al-Hiyasat et al., 2002)
		↓ epididymal sperm counts in 3500 ppm BPA- treatment group	(Tyl et al., 2008)
		Abnormal sperm morphology	(Toyama et al., 2004)
Testosterone Levels	C57BL/6 mice	↓ plasma testosterone levels	(Takao et al., 1999)

The lowest effective doses of BPA in laboratory animal studies range from μg/kg/d to mg/kg/d, but depend on the endpoint, the species and strain, and the type of study. This provides a caution that understanding of the biological system and conditions of exposure is critical to estimating the risk of adverse effects of this estrogenic agent, in laboratory animals and in extrapolating to marine organisms. In addition the extrapolation of administered dose across species, particularly between mammals and other major classes, requires careful consideration.

Human Studies

Only three studies associating BPA exposure with reproductive and developmental outcomes in humans were identified for this review. In a study of 77 women, higher serum BPA was found in women with a history of recurrent miscarriage than in controls (Sugiura-Ogasawara et al., 2005). In another study (Takeuchi et al., 2004) 19 women with polycystic ovary syndrome and 7 obese women were found to have higher serum BPA than 19 controls. Additionally, significant correlations were found between serum androgen measures and serum BPA. Another report from the same group (Takeuchi and Tsutsumi, 2002) found higher serum BPA in males than in either normal women or women with polycystic ovary syndrome and confirmed the correlation with testosterone across groups. A third study found lower concentrations of serum BPA in women with "complex endometrial hyperplasia with malignant potential" as compared to controls with normal endometrium or with "simple endometrial hyperplasia of a benign nature" (Hiroi et al., 2004). Once again these are associations and not sure how this will be linked with marine based outcomes.

Summary

Overall, data in laboratory animals show that exposure of males and females to BPA results in effects consistent with the estrogenic activity of BPA. Commonly reported effects in the adult female rodent reproductive system include an increase in uterine weight, changes in the uterine and vaginal epithelium, accelerated mammary gland development, younger age at first estrus

cycle, and earlier (younger age) vaginal opening. Having estrus cycles at a younger age coupled with younger age at time of vaginal opening are consistent with earlier pubertal onset. In males, prostate gland development was stimulated in terms of prostate weight as well as duct structure. Effects were also seen on the testis, seminal vesicles, spermatogonia, and testosterone level. Endpoints influenced by developmental BPA exposure include sex-differentiated emotional and cognitive behavior. Quantitative alterations such as anogenital distance and postnatal growth retardation have also been noted.

Although the bulk of the literature available comprises toxicological studies in laboratory rodents, the findings may be indicative of potential effects in marine organisms. BPA is "estrogenic" and may act through the estrogen receptor (ER). Estrogen receptors or other members of this family of nuclear receptors are present in all known vertebrates. Thus, terrestrial mammals and other vertebrates are likely to have several similarities with marine mammals and vertebrates, and effects in terrestrial species should be considered if sufficient empirical data in marine species is not available.

Cancer

Introduction

The potential carcinogenicity of a chemical is always a concern when the chemical is manufactured and used in high volumes. BPA has been investigated using the standard bioassay and though other studies.

Laboratory Rodent Studies

The National Toxicology Program (NTP) concluded from its analysis of data from a two-year carcinogenicity bioassay of BPA given orally to adult male and female mice and rats that "there was no convincing evidence that bisphenol A was carcinogenic to F344 rats or B6C3F1 mice of either sex" (NTP, 1982). Both male and female rats were fed diets containing 1,000 or 2,000 ppm BPA. Male mice were fed diets of 1,000 or 5,000 ppm BPA and female mice were given diets containing 5,000 or 10,0000 ppm BPA.

However, studies finding a higher incidence of neoplasia following prenatal or early-in-life exposure of rodents to BPA have been published. Neonatal male Sprague-Dawley rats were given subcutaneous injections containing 10 micrograms BPA per kg body weight in oil on postnatal days 1, 3 and 5. Control rats were injected with oil alone on these days. At 28 weeks, all animals were killed and prostate tissues were examined. Prostatic intraepithelial neoplasia, a lesion interpreted as precancerous were seen in 100 percent of the BPA-treated animals compared with 11 percent of the control animals (Ho et al., 2006; Keri et al., 2007; Prins et al., 2007; Prins et al., 2008). Female offspring of Wistar rats given 25 micrograms BPA per kg body weight from day 8 of pregnancy to day 22 had a higher incidence of precancerous mammary gland lesions in response to a dose of N-nitroso-N-methylurea than did females born to mothers that were not given BPA during pregnancy (Durando et al., 2007). However, BPA is genotoxic to mammalian cells. Incubation with BPA results in the formation of DNA adducts and reactive oxygen species within cultured cells.

BPA caused a "slight" increase in the production of hydroxyl radicals in the rat brain (Obata and Kubota, 2000). In a review of effects of chemicals on sulfotransferase activity, Wang and James (2006) identified BPA as a chemical that reduces the activity of phase 2 sulfotransferases (Wang and James, 2006). Therefore, by reducing the acitiviy of sulfotransferase enzymes BPA has the

potential to alter certain hormone levels and to reduce the rate of detoxification of some carcinogens and other toxic chemicals.

Effects in Cultured Mammalian Cells

The concentration of BPA that inhibits DNA synthesis or protein synthesis by 50 percent in cultured BALB/3T3 cells was estimated to be between 10 and 100 micromoles/L (2.3 and 23 mg/L) (Hanks et al., 1991). BPA at a concentration of 0.5 mmoles/L (114 mg/L) was lethal to cultured rat hepatocytes. Incubation of hepatocyte mitochondria with 114 mg/L BPA uncoupled adenosine triphosphate (ATP) synthesis from electron transport (Nakagawa and Tayama, 2000). Mouse Neuro2a cells and GC1 cells cultured in the presence of BPA produced reactive oxygen species. Incubation in the presence of BPA above 11 mg/L caused a decrease in the amount of mitochondrial complex 1 (Ooe et al., 2005). Incubation of human embryonic 293 cells with 11 mg/L BPA for 24 hours decreased cell viability (Benachour et al., 2007).

BPA produced chromosomal aberrations in Chinese hamster ovary (CHO) cells (Hilliard et al., 1998). Incubation of cell cultures with BPA resulted in the formation of DNA adducts. Bisphenol-o-quinone was isolated from cultured cells, and this oxidation product reacted with DNA to form two of the DNA adducts formed in cells cultured with BPA (Atkinson and Roy, 1995).

Dairkee et al. (2008) investigated the pattern of gene expression in epithelial and stromal cells from the breast contralateral to the one with cancer. When cultured in the presence of BPA, there was an increase in expression of genes associated with deregulation of the cell cycle and of genes associated with resistance to apoptosis. The level of expression of these genes was positively correlated with the aggressiveness of the breast cancer in the patient.

Summary

In a standard cancer bioassay, BPA was not considered carcinogenic in mice and rats given high daily doses. However, there is some evidence that BPA may be carcinogenic to new born animals. It has been shown that BPA can be genotoxic to mammalian cells in culture and intefer with some cellular precesses. Further investigation is needed to determine what, if any, role BPA may have in carcinogenisis.

Obesity

Introduction

Stemp-Morlock (2007) observed that the obesity rate has greatly increased over the past 20 years. An estimated one-third of U.S. adults are overweight and more than one-third of U.S. children are overweight or at risk for being overweight. There is a strong association between obesity and a number of health issues such as diabetes, coronary heart disease, hypertension, and gall bladder disease. Traditionally obesity has been viewed as a result of reduced physical activities and increased caloric intake. Data from recent studies, however, suggest that exposure to chemicals that perturb the critical pathways in adipogenesis, lipid metabolism or energy balance could also initiate or exacerbate obesity. BPA is one of the candidate chemicals that are now considered under the “environmental obesogen” hypothesis (Grun and Blumberg, 2007; Wada et al., 2007).

The study of environmental obesogen is an outgrowth of endocrine disruptor research. Hormones are key players in the development and maintenance of adipose tissues. In adults, sex steroids together with growth hormone have fat mobilizing properties (anti-adipogenic), whereas cortisol and insulin have lipogenic effects (Grun and Blumberg, 2007). Major targets for estrogen action in adipocytes include the reduction in lipogenesis via direct inhibition of adipocyte lipoprotein lipase expression (Homma et al., 2000). However, BPA is an example of a compound with ER agonist activity that behaves as an obesogen under specific conditions or when exposure occurs during sensitive developmental windows.

Laboratory Rodent Studies

Prenatal exposure of mice in range of 0.1 to 1.2 mg/kg-day of BPA led to significant weight gain (Rubin et al., 2001). Miyawaki et al. (2007) further demonstrated that exposure of mice to BPA from gestation day 10 to postnatal day 30 caused obesity and hyperlipidemia. In females, the mean body weight increased by 13 percent in the low dose (LD) group and 11 percent in the high dose group compared with the control group. The mean adipose tissue weight was higher by 132 percent in the LD group, while this tissue weight in the high dose (HD) group was not significantly higher than the control group. The mean cholesterol level was also higher by 33 percent in the LD group and 17 percent in the HD group. In males, the mean body weight and adipose tissue weight were higher by 22 percent and 59 percent, respectively, in the HD group compared to the control group; however, these weights in the LD group were not significantly higher. It is interesting to note that BPA caused a non-monotonic, inverted-U-shaped dose response in female offspring, but a monotonic dose response in the male offspring. A non-monotonic dose response was also shown in rats (Seidlova-Wuttke et al., 2005). Three-month old rats were ovariectomized and received 0, 33, or 333 µg/kg-day of BPA for three months. The paratibal fat depot, which is extremely sensitive to estrogen withdrawal (from ovariectomy), was measured. The size of the fat depot was significantly higher in the LD group but not in the HD group compared to the control group.

In vitro Studies

In vitro, BPA stimulated the accumulation of triacylglycerol in 3T3-L1 preadipocytes and hepatocytes (Wada et al., 2007). The lipid accumulation responses were time- and dose-dependent. Masuno et al. (2005) similarly observed that BPA increased the triacylglycerol content of 3T3-L1 cells, as well as increased the levels of lipoprotein lipase and adipocyte-specific fatty acid binding protein mRNAs. These findings indicate that BPA accelerated the terminal differentiation of 3T3-L1 cells into adipocytes. Interestingly, Phrakonkham et al. (2008) found that BPA did not enhance triglyceride accumulation in 3T3-L1 preadipocytes, but increased the expression of adipocyte differentiation genes. It was observed that BPA also enhanced glucose transport in adipocytes (Sakurai et al., 2004), which in turn may contribute to lipogenesis. It appears that the enhanced glucose uptake was a result of the upregulation of GLUT4, an insulin-regulated glucose transporter found in adipose tissues.

As discussed, insulin has a lipogenic effect. Adachi et al. (2005) investigated and found that BPA promoted insulin secretion in rat pancreatic islets. The authors pointed out that the insulin inducing effect could potentially cause hyperinsulinemia, resulting in obesity, exhaustion of pancreatic β-cells, and diabetes. In another study, Alonso-Magdalena et al. (2005) demonstrated that BPA suppressed low-glucose-induced intracellular calcium oscillations in mouse pancreatic α-cells, the signal that triggers glucagon secretion. Since glucagon has a lipolytic effect in

adipose tissue, the suppression of glucagon releases via calcium modulation would contribute to lipid accumulation.

Overall, it appears that BPA influences multiple biochemical processes that govern obesity. Mechanistic studies suggest that BPA, as a developmental obesogen, produce this effect via ER signaling and other pathways. Upregulation of insulin from pancreatic β-cells appears to be mediated by "traditional cytoplasmic/nuclear" ER (Adachi et al., 2005). BPA is reportedly capable of binding competitively to ER β. Addition of ICI 182780 (ICI), an ER blocker, significantly suppressed the observed insulin increases induced by BPA. The regulation of glucagon from pancreatic α-cells, however, seems to be mediated by a "non-classical membrane ER" (ncmER). The occurrence of a ncmER in the pancreas that was capable of mediating BPA actions was recently reviewed (Wetherill et al., 2007). Using immunocytochemical and biochemical techniques, Alonso-Magdalena et al. (2005) identified the receptor used by BPA in modulating calcium oscillations and glucagons levels is likely to be the same ncmER discussed in Wetherill's review article. With respect to upregulation of GLUT4, the insulin-regulated glucose transporter found in adipose tissues, in enhanced glucose uptake in adipocytes, Sakurai et al. (2004) used ICI to showed that this BPA action was not mediated by ERs. Because the increase in GLUT4 expression is positively associated with adipocyte differentiation (MacDougald and Lane, 1995) and the role of peroxisome proliferators-activated receptor-γ (PPAR-γ) in lipogenesis and adipose differentiation is well established (Kersten, 2002), the authors speculated that PPAR-γ may be involved in GLUT4 regulation. Phrakonkham et al. (2008) took one step further to investigate whether BPA would affect adipogenic transcription factors and biomarkers such as CCAAT/enhancer binding proteins (C/EBPβ, C/EBPδ), and PPAR-γ in 3T3-L1 preadipocytes. They confirmed that BPA upregulated the expression of these factors.

Human Studies

Human data on the relationship between BPA exposure and obesity are sparse. Non-occupational exposure to BPA in 20 women was investigated in Southeast Spain (Fernandez et al., 2007). The mean age was 59.7 and the body mass index (BMI) was 31.9 kg/m^2. The BMI data were consistent with the finding by the European Protective Investigation into Cancer and Nutrition in 2002 that suggested these women were overweight. BPA was detected in 55 percent of the adipose tissue samples. In a Japanese study the investigators compared the serum levels of BPA between non-obese and obese women (Takeuchi et al., 2004). Obesity was defined by a BMI equal to or greater than 25 kg/m^2. The non-obese group consisted of 19 women, with a mean age of 27.5 and BMI of 19.7; whereas the obese group consisted of seven women, with a mean age of 28.8 and BMI of 28.5. Takeuchi et al. found that BPA serum levels were significantly higher in the obese group ($P<0.05$), demonstrating a positive association between BPA and obesity in this study.

Summary

While human data on the relationship between BPA exposure and obesity are sparse, they do demonstrate a positive association. Under controlled experimental conditions, the rodent studies further establish the cause-effect relationship between BPA and obesity. Mechanistic studies have added to the weight of this evidence. Collectively, human and rodent data paint a picture

that BPA can potentially cause or contribute to human obesity, which in turn is a risk factor for diabetes, coronary heart disease, hypertension, and gall bladder disease.

Thyroid

Introduction

Thyroid hormones (THs), thyroxine (T4) and triiodothyronine (T3), have diverse functions. They are essential to brain development, influence growth via stimulation of growth hormone, and regulate basal metabolic rates, as well as lipid and carbohydrate metabolism (Greenspan and Gardner, 2003). Environmental chemicals can disrupt TH functions by preventing the biosynthesis via the inhibition of iodide uptake or thyroid peroxidase activity, interfering with the activity of transthyretin that transports of THs to target tissues, increasing the metabolism via deiodinases and uridine diphosphate glucuronyltransferase, or perturbing the binding to thyroid hormone receptors (TRs) (Zoeller, 2007). The resulting hypothyroidism or thyroid hormone dysregulations in adults may lead to fatigue, weight gain, weak pulse, cold intolerance, mental sluggishness, and depression. Such dysregulation during the perinatal period, on the other hand, could cause cretinism in the affected person, which is characterized by having a short stature, poor motor skills, moderate to severe mental retardation.

Laboratory Studies

Using rat liver cells, Moriyama et al. (2002) demonstrated that BPA interacted with both TRα and TRβ in inhibiting T3 stimulated response. The experimental findings led the authors to conclude that BPA could displace T3 from the TR and recruit a transcriptional repressor, resulting in gene suppression. BPA can antagonize T3 action at the transcriptional level. It should be noted that while some *in vitro* studies demonstrated that BPA is a TR antagonist (Kitamura et al., 2002; Kitamura et al., 2005; Moriyama et al., 2002), at least one study showed that BPA acts as an agonist (Ghisari and Bonefeld-Jorgensen, 2005). An *in vivo* study conducted by Iwamuro et al.(2003) found that BPA reduced the rate of metamorphosis in *Xenopus*. This finding seems to be consistent with the *in vitro* observation that BPA serves as a TR antagonist. However, mammalian studies suggest BPA's mechanism of action is much more complex. Zoeller et al. (2005) reported that BPA increased serum T4 in rat pups but also increased the expression of the RC3 gene in the dentate gyrus, part of the hippocampal formation. The investigators rationalized that the T4 increase was a result of BPA's antagonist action, competitively displacing T4 from TRβ. Because RC3 expression is directed by TRα, it was believed that BPA did not exert an antagonist action on TRα. In a prenatal study of brain development in mice, Nakamura et al. (2006a) found that growth in the ventricular zone of the BPA-treated offspring was decreased, whereas in the cortical plate growth was increased. In addition, the expression of TRα gene (and other genes) was significantly upregulated in the cortical area of the BPA-treated group. The authors' interpretation was that BPA affected cortical plate growth via the upregulation of the thyroid pathway. In doing so, BPA might have disrupted normal neocortical development by accelerating neuronal differentiation and migration.

Human Studies

BPA has been found in serum of pregnant women, in amniotic fluid and in cord blood and placenta (Ikezuki et al., 2002; Schonfelder et al., 2002). Exposure to BPA in utero could affect

TR and result in mental retardation and dwarfism similar to those caused by hypothyroidism during critical windows of development.

Summary

The resulting hypothyroidism or thyroid hormone dysregulations in adults may lead to fatigue, weight gain, weak pulse, cold intolerance, mental sluggishness, and depression. Such dysregulation during the perinatal period, on the other hand, could cause cretinism in the affected person, which is characterized by having a short stature, poor motor skills, moderate to severe mental retardation. There is some evidence that BPA can disrupt the function of thyroid hormones by blocking the hormone's binding to its receptor.

Immune System

Introduction

The immune system is our main defense mechanism against invading microorganisms or tumor growth. Suppressing the immune system may weaken our defense capabilities. Overstimulation of the immune system during an infection, however, can cause extensive collateral damages—"spill-over" destruction of surrounding but otherwise healthy tissues that may prove fatal in some instances. Dysregulation of the immune system in other situations may lead to autoimmunity—attacking "one's own tissues without cause or provocation."

The immune system is under tight, complex regulation to ensure that it continues to function at the optimal range. Existing data suggest that BPA could perturb this regulatory apparatus, leading to weakened defense capabilities or detrimental overstimulation of immune functions as an end result. It appears that BPA can either act directly or indirectly via the neuroendocrine system to affect the immune system. It has been known that both the thyroid and sex hormone neuroendocrine systems are" immunoregulators Berczi (1997), and it should not come as a surprise that BPA, which is known to disrupt thyroid and estrogen functions, can potentially impact the immune system.

Against the above background, it should be intuitive that BPA, which is known to disrupt thyroid and estrogen functions, can potentially impact the immune system. No literature was found on BPA's effects on the human immune system. Data from literature, however, indicate that current research focuses on the estrogenic effect of BPA on immune functions. In an *in vitro* system, Yamashita et al. (2002) using immune cells from BALB/c mice demonstrated that BPA enhanced innate immune response by increasing cytokine production including tumor necrosis factor (TNF) and IL-1 in macrophages, and stimulated both T and B cells in adaptive responses. The authors used IL-2 and IFN-γ as markers for Th1 response and IL-4 for Th2 response, and found that BPA stimulated Th1 cells to produce IFN-γ and Th2 cells to express IL-4. The authors concluded that BPA does not preferentially activate the Th1 or Th2 path. *In vivo*, BPA also enhanced Th1 or Th2 response, depending on the doses administered (Jontell et al., 1995; Tian et al., 2003; Yoshino et al., 2003). In addition, prenatal exposure to BPA was shown to augment both Th1 and Th2 responses in adulthood (Yoshino et al., 2004). BPA's effects on the immune system are discussed in more detail in the following sections.

Innate Immune Function

The innate immune system comprises the cells and mechanisms that defend the host from infection by other organisms, in a non-specific manner. Macrophages produce tumor necrosis

factor-α (TNF-α) and nitric oxide (NO) as part of the innate defense against bacteria including bacterial endotoxin. While TNF-α and NO play an important role in bacterial clearance, overproduction of these factors can be detrimental because of their cytotoxicity. For example, NO produces detrimental effects by generating oxidative stress or nitrating proteins and genes. Thus, either underproduction or overproduction of these factors can be harmful. Hong et al. (2004) showed that BPA enhanced NO production in lipopolysaccharide (LPS) induced macrophages *in vitro.* Further, Goto et al. (2004) demonstrated that macrophages were required for BPA-induced stimulation of murine splenic T cells. The data seem to suggest that enhanced T cell activities were a result of the modulation of macrophage cytokines by BPA. This observation is in agreement of the finding of Yamashita et al. (2002) on macrophages. In an *in vitro* system, Yamashita et al. using immune cells from BALB/c mice demonstrated that BPA enhanced innate immune response by increasing cytokine production including tumor necrosis factor (TNF) and IL-1 in macrophages.

A series of experiments, however, suggest that BPA could compromise innate immune function by down-regulation of TNF-α and NO in macrophages. The activation of the transcription factor NF-κB (Igarashi et al., 2006) and IFN-β promoter (Ohnishi et al., 2008) are essential for the production of TNF-α and NO. Igarashi et al. and Ohnishi et al. demonstrated that BPA inhibited LPS-induced activation of NF-κB and IFN-β promoter. Since LPS uses Toll-like receptors (TLR) to stimulate macrophages, the authors speculated that BPA may interfere with TLR signaling. There are also data to suggest the involvement of ERs in BPA inhibition of LPS-induced NO and/or TNF-α production (Kim and Jeong, 2003; Yoshitake et al., 2008). Kim and Jeong (2003) especially showed that BPA inhibited LPS-induced TNF-α and NO synthesis via the decrease in the levels of TNF-α and inducible nitric oxide synthase (iNOS) mRNA. Treatment of ICI, an ER antagonist, inhibited the suppressive effect of BPA.

BPA also seems to have a negative effect on the recruitment of macrophages into tissues, which is an important process in innate host defense. Monocyte chemoattractant protein-1 (MCP-1), a member of the chemokine family, plays a pivotal role in recruiting blood monocytes to become tissue macrophages during innate immune responses. Various cells including fibroblast, vascular endothelial cells, smooth muscle cells, and macrophages produce MCP-1 in response to stimuli from LPS, IL-1 and TNF-α. BPA was shown to decrease MCP-1 levels in a dose-dependent manner in human breast cancer cell line MCF-7 that express ER (Inadera et al., 2000).

In summary, BPA may upregulate or down-regulate macrophage functions. Either case could produce a harmful effect.

Adaptive Immune Function

The adaptive immune system is composed of highly specialized, systemic cells and processes that eliminate or prevent pathogenic infestation. Data from *in vitro* studies of various cell lines and *in viv*o rodent studies demonstrated clearly that BPA can modulate adaptive immune functions. Because humans and rodents have similar patterns of immune development (Holladay and Smialowicz, 2000), an inference can be drawn that BPA may also affect the human immune system. The adaptive immunity works in concert with the innate immunity to protect the body against pathogens and tumors. Interfering with the programming of the Th1 or Th2 pathway during development may have dire consequences—reduced ability to fight certain infections, allergy, or autoimmune disorder.

Various effects of BPA on Th1 and Th2 immune responses have been reported. Most of these effects are significant; however, the data do not paint a consistent picture. Sakazaki et al. (2002) observed the presence of ERα in mouse splenic lymphocytes and reported that BPA strongly suppressed LPS-induced B cell proliferation relative to concanavalin A (con A) induced T cell mitogenesis. On the other hand, BPA greatly enhanced immunoglobin IgG2a antibodies and IFN-γ (indicators of Th1 or T cell response) and moderately increased IgG1 and IL-4 (indicators of Th2 or B cell response) in mice that were immunized with hen egg lysozyme (Yoshino et al., 2003). Prenatal exposure of mice to BPA also caused an up-regulation of Th1 and Th2 responses in adulthood; however, the Th1 response was much more significant (Yoshino et al., 2004).

Tian et al.(2003b) reported that BPA selectively promoted the Th2 immune response in mice infected with Trichinella spiralis. However, Youn et al. (2002) showed that after four weeks of treatment in male ICR mice, BPA induced prolactin production in spleen and caused a shift of cytokines from the Th2 to Th1 type. Goto et al. (2007) also reported that exposure of BPA to mice via the oral route caused a shift of the Th2 cytokine profile to Th1. BPA moderately reduced IL-4 levels but increased IFN-γ. IgG2a, a representative of Th1 type antibody, was also augmented.

Because BPA as a xenoestrogen can modify the Th1/Th2 ratio and estrogen appears to provide a link between Th1 or Th2 cytokines and systemic lupus erythematosus (SLE), several studies investigated the possible role of BPA in this autoimmune disease in a murine model. Sawai et al. (2003) make several observations to build the association of estrogen and Th1 cytokines to SLE. SLE occurs at a ratio of more than 8:1 in females compared with males and commonly strikes in women during the childbearing years when circulating estrogen levels are highest. Patients with SLE have ongoing interferon-α (IFN-α) production and serum IFN-α levels are correlated with both disease activity and severity (Ronnblom and Alm, 2003). SLE is characterized by high levels of IgG autoantibodies and glomerulonephritis. In the murine model, the isotype switching to IgG2a, which contributes to glomerulonephritis, is IFN-γ (a Th1 cytokine) dependent (Haas et al., 1997). In the Sawai et al. study, the authors observed that BPA inhibited IFN-γ production and delayed proteinuria development. The authors concluded that BPA acted in a protective manner in SLE-prone mice—it is likely that the decreased in IFN-γ levels contributed to a reduction in isotype switching to IgG2a, which in turn prolonged the symptom-free period. On the other hand, Kudaeva et al. (2005) found that BPA caused a higher incidence of glomerulonephritis in their SLE model, suggesting that the disease is driven by Th2 cytokines instead. As Miyake et al. (2002) observed the roles of Th1 and Th2 cytokines in the pathogenesis of SLE are still in debate. Certain SLE patients have high levels of Th2 cytokines such as IL-4, IL-6, and IL-10, while other patients have high levels of Th1 cytokines such as IFN-γ.

The pathogenesis of allergic diseases is associated with the up-regulation of allergen-specific IgE, which is driven by the Th2 path (Offit and Hackett, 2003). Since BPA can affect the Th2 and Th1 pathways, its role in modulating the levels of IgE have been investigated. Lee et al.(2003) reported that BPA significantly enhanced IL-4 production in keyhole limpet hemocyanin-primed T helper (Th) cells in a concentration dependent manner. They also showed that BPA *in vivo* significantly increased IL-4 production and IgE levels in sera of keyhole limpet hemocyanin-primed mice. This suggests that BPA drove the Th2 path in up-regulating the IgE levels. However, the findings of Alizadeh et al. (2006) disagree in part with those of Lee et al.

Alizadeh et al. reported that BPA lowered the titer of IgE while enhancing the levels of IFN-γ and IgG2a. They also observed that the IL-4 levels were unchanged. This suggests that BPA modified the Th1 path in affecting the IgE levels. However, Alizadeh et al. pointed out that the dose of BPA used in their study was higher than that used in the Lee et al. study. Looking at BPA's possible effect on allergy from a different angle, Ohshima et al. (2007) examined whether prenatal exposure to BPA would influence the acquisition of an allergic predisposition. The investigators showed that offspring mice from the BPA treatment group, when challenged with ovalbumin (a food antigen), retained a higher antigen-specific T cell proliferation rate, had higher levels of ovalbumin-specific IgG1 and IgG2a, but failed to accumulate regulatory T cells. Ohshima et al. concluded that BPA may interfere with the development of oral tolerance and lead to the emergence of food allergies.

Summary

BPA appears to possess complex immuno-modulating effects. It may stimulate or suppress the immune system. It may also alter immune response pathways. BPA's immunosuppressive effects can potentially compromise our abilities to flight infections. It is more difficult to interpret BPA's immune-stimulative effects. Existing data do not provide conclusive evidence that such stimulatory effects can predispose the affected individuals to autoimmunity or allergy.

Nervous System

Introduction

BPA has both indirect and direct effects on the nevous system. Since gonadal hormones in conjunction with other neurotrophins regulate cell death, neuronal migration neurogenesis, and neurotransmitter plasticity, BPA, in disrupting sex hormone functions, can affect brain development (Simerly, 2002). In disrupting thyroid functions, BPA can also affect the development of the nervous system because thyroid hormones play an important role in prenatal and neonatal development of the brain (Porterfield and Hendrich, 1993). Early hypothyroidism, for example, caused stunted dentritic growth in hippocampal CA3 neurons, resulting in cognitive effects including impaired memory, spatial perception, and attention problems (Schantz and Widholm, 2001). In addition, BPA may directly cause neurodegeneration. BPA was shown to produce oxidative stress and induce apoptosis in neuronal cells (Lin et al., 2006b). Experimental data from literature indicate that BPA has a significant impact on the dopaminergic system and hippocampal associated cognitive functions, as well as having a neurodegenerative effect. The following is a technical synopsis, detailing the effects of BPA on the nervous system.

Dopaminergic System

The phenotypic expression of behaviors is the outcome of interacting cortical neuronal networks that are modulated by subcortical components such as the cholinergic neurons of Myenert's basal nucleus, dopaminergic neurons of the Ventral Tegmental Area (VTA), serotongeric neurons in the Raphe nuclei, norepinephrine neurons in the Locus Coeruleus, and histamine neurons in the posterior hypothalamus (Viggiano et al., 2003). Though behaviors emerge from complex interactions, the dopamine systems are very important for the phenotypic expression of attention and reward. It is recognized that the mesolimbic VTA and the nigrostriatal dopaminergic sytems are essential to reward-based learning, novelty-induced behavior, attention, and activity (Andersen and Teicher, 2000; Berridge and Robinson, 1998; Carlsson, 1993). The dysfunction of dopaminergic systems has been associated with neuropsychiatric disorders such as

Parkinson's disease, schizophrenia, attention deficit/hyperactivity (ADHD), and autism. It is interesting to note that autism and ADHD have a commonality-- that both diseases cause effects on gross and fine motor skills as well as the impulsive driven behaviors. Certain drugs used to treat schizophrenia and ADHD, for example, target the dopamine system. Most of the anti-psychotic medications for schizophrenia are dopamine receptor antagonists, whereas drugs for treating ADHD are usually psycho-stimulants that modify dopamine transmission (Viggiano et al., 2003). Methylphenidate, which blocks dopamine re-uptake and effectively increases the synaptic concentration of dopamine, has been used to treat ADHD (Medscape, 2006). Addictive drugs such as cocaine and amphetamine, on the other hand, create a "reward" reinforced behavior by modifying the dopaminergic transmission of the VTA.

Sex differences in striatal dopamine content or density of dopamine-1 and dopamine-2 (D_1 and D_2) receptors during development suggest that sex steroid hormones may mediate the development of dopamine systems in the brain (Andersen and Teicher, 2000; Ferretti et al., 1992). In adults, estrogen appears to be neuroprotective (Marx and Lieberman, 1998). Prenatal "excess" exposure to estrogen seems to have an opposite effect than in adulthood. That evidence was seen in psychotic patients prenatally exposed to diethylstilbestrol (DES) (Katz et al., 1987). On the other hand, Turner syndrome (XO), in which a missing X chromosome that causes an absence of estrogen during perinatal life, is associated with cognitive problems and psychosis (Bamrah and Mackay, 1989).

Some evidence suggests that BPA can affect the dopaminergic systems via the endocrine mechanism. Prenatal and neonatal exposure to BPA was shown to alter D_1 receptor expression and density in male mice, which in turn led to the enhancement of D_1 receptor-dependent rewarding effect induced by methamphetamine (Suzuki et al., 2003b). Laviola et al. observed that BPA affected the development of the dopamine pathways in a sex-linked manner (2005). Prenatal exposure of mice to BPA appeared to have blunted the development of the dopaminergic "reward" pathway in the female offspring (but not the male offspring). The treated adult female offspring no longer displayed an amphetamine reinforced behavior.

Because of the interest in BPA's possible ADHD effect, much of the research deals with BPA and hyperactivity behaviors in experimental animals. It is unclear whether the dopamine systems are hyper or hypofunctioning in ADHD. Evidence that support the dopamine system hypofunctioning theory includes the use of methylphenidate, a dopamine re-uptake blocker, to ameliorate ADHD symptoms and the observation of induced hyperactivity by chemical produced lesions (dopamine deficits) in the striatum (Papa et al., 2000; Sagvolden et al., 1992). On the other hand, the observation that many dopamine receptor knockout (KO) mice are hypoactive and that dopamine transporter KO mice are hyperactive seem to suggest that ADHD is related to dopamine system hyperfunctioning (Viggiano et al., 2003). In the hypofunctioning model, one would expect to observe hyperactivity when dopamine hypofunctioning were created by the dopamine receptor knockout. Instead, hypoactivity was observed. Likewise, one would expect to observe hypoactivity when hyperfunctioning of the dopamine system were created by the dopamine transporter knockout in the hypofunctioning model. Instead, hyperactivity was observed. In all, the knockout experiments appear to support that ADHD is associated with the hyperfunctioning of the dopamine system. Research data on BPA reflect these observations. They either support the hyperfunctioning theory or the hypofunctioning theory. While further research is required to clarify the mechanism(s) of action of BPA on the dopamine system, it is clear that BPA adversely impacts the dopamine system in the animal model.

A series of studies demonstrated that prenatal and neonatal exposure to BPA upregulated activities of the dopamine system and produced hyperactivity or enhanced rewarding effects induced by drugs of abuse. Suzuki et al.(2003b) showed that prenatal and neonatal exposure of mice to BPA caused upregulation of dopamine D_1 receptors and produced hyperlocomotion and increased rewarding responses induced by methamphetamine. In addition, BPA exposure produced a significant increase in levels of D_1 mRNA. In characterizing the window of vulnerability in development, Narita et al. (2007) demonstrated that exposure of mice to BPA during either organogenesis or lactation, but not implantation and parturition, significantly enhanced the morphine induced hyperactivity and rewarding effects. Narita et al. further showed that exposure to BPA during organogenesis or lactation caused an upregulation of dopamine receptor function to activate G-protein, short for guanine binding proteins that function as "molecular switches" to regulate downstream processes, in the mouse limbic forebrain. Mizuo et al. (2004a), on the other hand, found that dopamine D_3 receptor-mediated G-protein activation was attenuated in mice exposed to BPA prenatally and neonatally. D_3 receptor activities contribute to the inhibitory modulation of D_1 and D_2 receptors (Mizuo et al., 2004b); thus the down-regulation of D_3 receptors can be interpreted as an upregulation of the overall dopamine function. In a rat model, Ishido et al. (2005) demonstrated that neonatal exposure to BPA caused significant hyperactivity at 4-5 weeks of age, and significantly decreased gene expression of dopamine transporter at eight weeks. All these experimental data lend support to the BPA-induced dopamine hyperfunctioning theory in ADHD.

However, there are also data that support the BPA-induced dopamine hypofunctioning theory in ADHD. Intracisternal administration of BPA to neonatal rats caused a deficit in dopamine neurons and a concomitant increase in motor activity (Ishido et al., 2004; Masuo et al., 2004). The effect of BPA on hyperactivity was dose-dependent when measured at 4-5 weeks. The dopamine deficit was indicated by a decrease in tyrosine hydroxylase, an important enzyme in the synthesis of dopamine, immunoreactivity. In a followup study, Ishido et al. (2007) demonstrated that oral administration of BPA to neonatal rats also caused hyperactivity and a significant reduction in tyrosine hydroxylase immunoreactivity.

Without doubt, there will be continuing debates on BPA's mechanisms of action on the dopamine systems. However, it is important to underscore the adverse impact of BPA on dopamine pathways in animal models, and the implication of BPA as a factor in the pathogenesis of disorders such as ADHD.

Hippocampus

The hippocampus, which is a scrolled structure located in the medial temporal lobe of the brain, plays an important role in declarative memory (Eichenbaum, 2004; Molavi, 1977). The hippocampus consists of morphologically distinct areas including the dentate gyrus and Cornu Ammonis (CA) zones (of which CA1 and CA3 are the largest). Declarative memory represents the ability to form memory of everyday facts and events through personal experiences that in turn help construct reality within consciousness. Thus declarative memory is more than the filing and recalling isolated events; it involves a series of cognitive processes—associative representation, sequential organization and relational networking—in relating past experiences to current perceptions in the construct of new memories as learning. The hippocampus files new memories, experiences, or learning as they occur, including spatial learning (Molavi, 1977; Schantz and Widholm, 2001).

Sex hormones play an important role in the hippocampus development, which is known to be a sexually dimorphic area in the brain (Goldstein et al., 2001; Tabibnia et al., 1999). Differential programming in the hippocampus by sex hormones can be illustrated by the observation that men generally outperform women on tasks that require spatial skills (Schantz and Widholm, 2001). As discussed, thyroid hormones are also important in the growth and maturation of the hippocampus. There is a clear concern that BPA, which has been shown to disrupt estrogen and thyroid functions, can potentially impact hippocampal development and function. The animal data summarized below suggest that BPA can adversely affect the hippocampus. It is not well understood, however, if these effects are mediated by endocrine disruption during development of the hippocampus.

In a mouse model, Miyagawa et al. (2007) measured learning behaviors and choline acetyltransferase (ChAT) in the hippocampus using 7-11 week old male mice that had been prenatally and neonatally exposed to BPA. Immunohistochemical measurements demonstrated a dramatic decrease in levels of ChAT in both low and high dose treatment groups. ChAT is an excellent biomarker to indicate the severity of memory loss because among the cholinergic parameters described for the brains of Alzheimer's disease patients, the decrease in ChAT is most prominent (Bartus et al., 1982; Dutar et al., 1995). Memory impairment by BPA was also shown in the step-through passive avoidance behavioral test. In a Morris Water Maze study, Carr et al. (2003) investigated BPA's effect on spatial learning. Neonatal mice were exposed to BPA and testing was performed between postnatal days 34-37. As expected, acquisition of maze performance was significantly better in control males than in control females. However, this gender-dependent pattern of acquisition was abolished in the low-dose group. This suggests that BPA has an effect on the development of this sexually dimorphic memory/learning center. In a perinatal rat study, Xu et al. (2007) investigated the possible role of thyroid hormone in spatial learning. Significant sex difference on behaviors was observed, as indicated by impaired spatial learning/memory in male pups after matured. They also found male rats to exhibit a transient hyperthyroidism followed by hypothyroidism. However the expression of thyroid hormone receptors and receptor responsive element in the developing hippocampus were not affected by BPA. Thus the involvement of thyroid hormone in this case remains equivocal. In another rat model, MacLusky et al. (2005) demonstrated that treatment of ovariectomized females with BPA dose-dependently inhibited the estrogen-induced formation of CA1 pyramidal cell dentritic spine synapses. The implication is that BPA exposure may interfere with the development and expression of normal sex differences in cognitive function, via inhibition of estrogen-dependent hippocampal synapse formation. Ogiue-Ikeda et al. (2008) investigated the rapid modulation of synaptic plasticity in adult male rat hippocampus. BPA was shown to significantly enhance long-term depression (LTD) in both CA1 and CA3 but suppressed LTD in the dentate gyrus of the hippocampus. In memory processing, both long-term potentiation (LTP) and LTD are essential. LTD may be a mechanism used to correct wrong memories formed by LTP.

Neuronal Apoptosis

Programmed apoptosis is a part of the maturation process that is essential for brain development. However, "unscheduled" apoptosis leads to neurodegeneration. Estrogen has been suggested to protect against neurodegeneration (Birge, 1997; Tang et al., 1996). In postmenopausal women who have decreased estrogen levels, the risk of Alzheimer's disease tends to increase, and replacement therapy with Tamoxifen reduces the risk. Tamoxifen appears to induce glutathione peroxidase, catalase, and superoxide dimutase in post menopausal women, and inhibit lipid

peroxidation (Thangaraju et al., 1994). Accordingly it is expected that tamoxifen would reduce oxidative stress associated with neuronal apoptosis.

As a xenoestrogen, BPA may have both anti-apoptotic and apoptotic properties. BPA was shown to increase hydroxyl radical formation in the rat striatum (Obata and Kubota, 2000), and enhance hydroxyl radical formation induced by 1-methyl-4-phenylpyridinium ion (MPP+) (Obata, 2006), known to cause neurodegeneration of the substantia nigra and produce acute Parkinsonian symptoms. More direct evidence on BPA's apoptotic property comes from the following studies. BPA was shown to increase intracellular reactive oxygen species and induce apoptosis in mesencephalic neuronal cell culture (Lin et al., 2006a). Lee et al. (2007) demonstrated that BPA increased apoptosis in PC12 cells and cortical neuronal cells. The BPA effect seems to be ER independent because ER antagonists, ICI and tamoxifen, did not block the apoptotic effect. Oka et al. (2003) further observed that BPA induces apoptosis in central neural cells during early Xenopus development and this effect appeared to be due to non-estrogenic activity on the developmental process. In studying hippocampal and cortical neurons, Negishi et al. (2003a), however, showed that BPA significantly inhibited the staurosporine-induced increase in caspase-3 activities. Their interruption was that BPA in such action may impede normal brain development by inhibiting desirable neuronal cell death via interference with caspase activities.

Summary

The implication of BPA's apoptotic property is that exposure to BPA may cause premature neuronal cell death. In that vein, BPA may be a risk factor for a wide range of neurodegenerative diseases. Laboratory animal data also suggest that BPA can specifically affect the dopamine system and hippocampus. Since the dysfunction of dopaminergic systems has been associated with neuropsychiatric disorders such as attention deficit/hyperactivity and autism, the concern is that BPA may be a factor in the pathogenesis of such disorders. Adverse impacts of BPA on the hippocampus, on the other hand, would compromise memory and learning. While these neurological studies provide some evidence that BPA has the potential to indirectly or directly affect the nervous system, much further research is needed.

Conclusions

Findings

This toxicological profile on BPA describes its effects on freshwater and marine life, humans, and laboratory animals.

- Most of the environmental concentration data are from fresh water systems. It would be useful to gather data on BPA prevalence in marine environments, especially near municipal and industrial outfalls, landfills, and other possible point sources of BPA.
- Most studies on the toxic effects of BPA on fresh water and marine organisms are short-term laboratory studies involving a single species. BPA induces endocrine manifestations, malformations, changes in growth, chromosomal damage, biochemical changes and, at sufficiently high concentrations, mortality. Adverse effects in benthic organisms have not been well studied. Benthic (sediment-dwelling) organisms are likely to receive much higher exposures, since BPA concentrations are higher in sediment than in the water column. The potential for adverse effects at lower aqueous concentrations when the exposure is longer-term and/or via the food web remain largely unexplored.

- Most of the effects identified at the lowest environmental concentrations are reproductive effects; there are adequate data to support the conclusion that BPA is a reproductive toxicant in the aquatic environment.
- Data in laboratory rodents show that exposure of males and females to BPA results in effects consistent with the estrogenic activity of BPA and likely acts through the estrogen receptor (ER). Estrogen receptors or other members of this family of nuclear receptors are present in all known vertebrates. Reported effects in the adult female rodent reproductive system include an increase in uterine weight, changes in the uterine and vaginal epithelium, accelerated mammary gland development, younger age at first estrus cycle, and earlier (younger age) vaginal opening. In males, prostate gland development was stimulated in terms of prostate weight as well as duct structure. Effects were also seen on the testis, seminal vesicles, spermatogonia, and testosterone level. Although the bulk of the literature available comprises toxicological studies in laboratory rodents, the findings may be indicative of potential effects in marine organisms.
- BPA was not considered carcinogenic in mice and rats given high daily doses. However, other studies still raise questions. Further investigation is needed to determine what, if any, role BPA may have in carcinogenisis.
- There is some evidence that BPA can disrupt the function of thyroid hormones by blocking the hormone's binding to its receptor.
- BPA appears to possess complex immuno-modulating effects. It may stimulate or suppress the immune system. Its immunosuppressive effects can potentially compromise an organism's abilities to flight infections. It is more difficult to interpret BPA's immune-stimulative effects.
- Laboratory animal data also suggest that BPA can specifically affect the dopamine system and hippocampus. While these neurological studies provide some evidence that BPA has the potential to indirectly or directly affect the nervous system, much further research is needed.

Data Gaps

- BPA is found in the water at the discharge for certain industries and treatment/landfill waste facilities, but it was not determined if there is general contamination away from the sources.
- The threat to aquatic life from the levels away from discharge sources are unknown.
- It has not been determined whether sediment concentrations are a greater concern than the levels in the water column
- While there are effects seen in animal studies, there is little evidence available and few studies of effects in humans.
- Sufficient evidence exists to identify BPA as causing developmental and immunological effects possibly through action on the endocrine system at higher levels, but the effects at environmental levels are less clear.

Recommendations

- Identify which aquatic species are most at risk to environmental BPA levels.
- Develop a full toxicological assessment on BPA to determine an acceptable fresh water and marine exposure level.
- Determine if environmental BPA concentrations, water and sediment, away from point and area sources are a threat to aquatic species.

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Appendix 1: Bisphenol A effects on aquatic organisms

Might want to state (as in Tables 2 & 3) that this is largely based on Kang et al 2007a)

Species	BPA exposure	Effect	Reference
Reproductive Effects			
Goldfish (*Carassius auratus)*	1 µM for 8 days	Vitellogenin induction	(Suzuki et al., 2003a)
Zebrafish (*Danio rerio)*	1000 µg/L for 3 weeks	Vitellogenin induction	(Van den Belt et al., 2003)
Swordtail (*Xiphophorus helleri)*	2000 µg/L for 3 days	Vitellogenin mRNA expression	(Kwak et al., 2001)
	2000 µg/L for 60 days	Induction of apoptosis in fish testis cells	
Fathead minnow (*Pimephales promelas)*	119–205 µg/L for 2 weeks	Vitellogenin induction	(Brian et al., 2005)
	640 & 1280 µg/L for 43 days 60 µg/L for 71 days	Vitellogenin induction	(Sohoni et al., 2001)
	640 & 1280 µg/L for 164 days	Inhibition of gonadal growth ♀ & ♂ ↓ egg production & F1 hatchability	
	16–1280 µg/L for 164 days	Inhibition of spermatogenesis	
Japanese Medaka (*Oryzias latipes)*	1820 µg/L for 60 days	Induction of testis–ova	Yokota et al., 2000
	10 µg/L 100 days post-hatch	Induction of testis–ova	(Metcalfe et al., 2001)
	837–3120 µg/L for 3 weeks	Induction of Vitellogenin and testis–ova	(Kang et al., 2002)
	10 µg/L for 4 weeks 100 µg/L for 2 weeks	Induction of female-specific proteins	(Kashiwada et al., 2002)
	10 µM for 2 weeks	Reduced number of eggs and hatchings	(Shioda and Wakabayashi, 2000)
	100–500 µg/L for 6 days	Choriogenin L mRNA expression	(Lee et al., 2002)
	500 µg/L for 6 days	Choriogenin H mRNA expression	
	500 – 1000 µg/L 1-5 weeks	Increased serum vitelloginen	(Tabata et al., 2004)
	500 - 1000 µg/L dichloroBPA	Increased serum vitelloginen	
	1000 µg/L for 5 weeks	Vitellogenin induction	
Medaka (*Oryzias latipes)*	200 µg/L for 15 days	Embryo lesions/swim-up failure	Zha and Wang, 2006
Medaka	200 µg/L for 9 days	Embryonic deformity	(Pastva et al., 2001)
Brown trout (*Salmo trutta f fario)*	1.75–2.4 µg/L for 2 months	Male: ↓ sperm density & motility Female: delayed ovulation	(Lahnsteiner et al., 2005)
	5 µg/L for 2 months	Male: ↓semen mass Female: No ovulation	
Rainbow trout (O *mykiss)*	70–500 µg/L for 6 & 12 days	Vitellogenin induction	(Lindholst et al., 2000)
Landlocked salmon (*Salmo salar* m. *Sebago*) yolk-sac fry	1000 µg/L at 6 days	Yolk-sac edema & hemorrhages	(Honkanen et al., 2004)
Atlantic salmon (*Salmo salar*)	25,000 or 125,000 µg/kg for 1 week	Induction of vitellogenin & eggshell zona radiata protein	(Arukwe et al., 2000)

Species	BPA exposure	Effect	Reference
Guppy (*Poecilia reticulata)*	274 & 549 µg/L for 21 days	Reduction of total sperm counts	Haubruge et al., 2000
Turbot (*Psetta maxima)*	59 µg/L for 3 weeks	Reduction of testosterone and 11-ketotestosterone, but induction of estrone	(Labadie and Budzinski, 2006)
	59 µg/L for 3 weeks	ZRP induction	(Larsen et al., 2006)
Cod (*Gadus moruha*)	59 µg/L for 3 weeks	ZRP & Vitellogenin induction	(Larsen et al., 2006)
Bream (*Abramis brama)*	10–50 µM	Vitellogenin induction	(Rankouhi et al., 2004)
African clawed frog (*Xenopus laevis*)	0.1 µM for 12 weeks	Feminization (female phenotype)	(Kloas et al., 1999)
Xenopus laevis tadpole	*0.01 or 0.1 µM for 120 days*	Feminization	(Levy et al., 2004)
Frog (*Bombina orientalis)*	100,000 µg/kg body weight	Liver vitellogenin mRNA induction in males:	(Gye and Kim, 2005)
Caiman latirostris	140 mg/L @ 33°C	Complete sex reversal	(Stoker et al., 2003)
Mussel (*Mytilus edulis)*	50 µg/L for 3 weeks	Gonad resorption	(Ortiz-Zarragoitia and Cajaraville, 2006)
Freshwater ramshorn snail (*Marisa cornuarietis)*	1–100 µg/L for 5 mo	♀: enlarged accessory pallial sex glands, ↑ oocyte production. ♂: ↓ ripe sperm in vesicula seminalis	(Oehlmann et al., 2000)
	100 µg/L for 12 mo	Induction of imposex intensities	
	0.05 & 1 µg/L (but not 0.1 µg/L) for 6 months	Superfemales with oviduct malformations	(Oehlmann et al., 2006)
	0.1 - 1 µg/L for 5 months	Induction of egg &clutch production; oviduct malformations	
Marine dogwhelk (*Nucella lapillus*)	1–100 µg/L for 5 months	♀enlarged accessory pallial sex glands and increased oocyte production ♂: reduction of penis length, prostate gland, & ripe sperm in vesicula seminalis	(Oehlmann et al., 2000)
Mudsnail (*Potamopyrgus antipodarum)*	30, 100, and 300 µg/kg dry sediment	Induction of unshelled embryos and embryo production	(Duft et al., 2003)
	1–100 µg/L for 21–63 days	Induction of embryo production	(Jobling et al., 2003)
Copepod (*Acartia tonsa)*	0.2, 2 and 20 µg/L for 10 days (not statistically significant at 0.2, and 2 µg/L)	Induction of egg production, a measure of maturation of female reproductive organs	(Andersen et al., 1999)
Aquatic insect (*Chironomus riparius)*	0.078–750 µg/L for 20 h	Delayed emergence of f_2 males & females	(Watts et al., 2001a)
	10,400 µg/L for 20 h	80% emergence of f_1 generation; no egg hatching & no emergence in f_2 generation	
Freshwater sponges (*Eunapius fragilis* & *)*Heteromyenia sp	16,000 µg/L for 6 days	Abnormal growth	(Hill et al., 2002)
	80000 & 160,000 µg/L 6 days	Complete inhibition of germination	

Species	BPA exposure	Effect	Reference
Hydra oligactis	≥1000 µg/L for 35 days	Suppression of testis formation	(Fukuhori et al., 2005)
	500 - 1000 µg/L for 35 days	Induction of asexual reproduction	
	500-3000 µg/L for 35 days	Suppression of sexual reproduction (more severe at 500 - 1000 µg/L)	
Other Effects			
Goldfish (*Carassius auratus)*	1 µM for 8 days	Reduced plasma Ca level & calcitonin secretion.	(Suzuki et al., 2003a)
Teleost Fish (*Coris julis)*	80,000 µg/L for 2 weeks	Induction of binding levels of somatostatin receptor subtype 2 Decreased levels of subtype 5	(Alo et al., 2005)
Zebrafish	7.8 µg/L	Decreased survival	(Yeo and Kang, 2006)
Goldfish (*Carassius auratus)*	10 µM for 6 h	Suppression of tartrate-resistant acid phosphatase & alkaline phosphatase b	(Suzuki and Hattori, 2003)
Fathead minnow	640 &1280 µg/L for 71-164 days	Inhibition of somatic growth in male	(Sohoni et al., 2001)
Zebrafish	10-20 µM for 72 h after fertilization	Upregulation of brain aromatase isoform (P450aromB) mRNA. Increased mortality. Increased incidence of curved tails	Kishida et al., 2001
Atlantic salmon (*Salmo salar*)	5000 µg/kg for 1 week	Reduction of 7-ethoxyresorufin *O-deethylase activity*	(Arukwe et al., 2000)
Landlocked salmon (*Salmo salar* m. *Sebago)*	100 & 1000 µg/L at 42 days	Stained fragments in hepatocyte nuclei	(Honkanen et al., 2004)
Turbot (*Psetta maxima)*	50 µg/L for 3 weeks	chromosomal damage in erythrocytes	Bolognesi et al., 2006
(Hermaphroditic fish Rivulus *marmoratus)*	600 µg/L for 96 h	Up-regulation of brain aromatoase *rm-cyp19b and ovarian rm-cyp 19a*	(Lee et al., 2006)
Xenopus laevis embryo	25–35 µM for 120 h	>75% mortality	(Iwamuro et al., 2003)
	10–20 µM for 7 days post-fertilization	Scoliosis and malformation of the head	
Xenopus laevis larvae	10–25 µM for 21 days	Suppressed spontaneous & thyroxin induced metamorphosis. Suppressed thyroxin receptor β gene expression	(Iwamuro et al., 2003)
Xenopus laevis embryo	20 µM for stage 6–10	Malformation and apoptosis of central nervous system cells	(Oka et al., 2003)

Species	BPA exposure	Effect	Reference
Xenopus laevis embryo	20 µM for 96 h after fertilization	Mortality, short body length, microcephaly, flexure, edema, and abnormal gut coiling	(Oka et al., 2003)
European common frog (*Rana temporaria)* embryo	10–1000 µg/L for 20 days w/ or w/o ultraviolet-B	*>90% mortality* @ 10–1000 µg/L *with UVB* 75% mortality at 1000 µg/L w/o UVB	(Koponen and Kukkonen, 2002)
	1000 µg/L for 10 da w/ UVB	100% developmental malformation	
Black-spotted pond frog (*Rana nigromaculata)*	200 µg/L for 45 days	Malformation of tail flexure	Yang et al., 2005
	20 and 200 µg/L for 60 days	Induction of total thyroxine	
Tago's brown frog (*Rana tagoi*)	1 µM for 72 h	Inhibition of thyroid hormone activity by reducing expression of preprotemporin-1TGb and 1Tga genes	(Ohnuma et al., 2006)
Hydra vulgaris	*>460 µg/L for 72 h*	Inhibition of regeneration in isolated digestive regions	(Pascoe et al., 2002)
Apple snail (*Marisa cornuarietis)*	100 µg/L for 9 days	Reduction of heart rate	(Schirling et al., 2006)
	50 -100 µg/L for 11–13 days	Induction of weight of hatched individuals	
Chironomus riparius	1000 µg/L for 2 days	Reduced wet weight. Delayed moulting	(Watts et al., 2001b ; 2003)
	>0.01 µg/L for 2 days	Induction of mouthpart deformities	
Copepod (*Acartia tonsa*)	20 (nonsignificant effect @ 2)	Accelerated egg production	(Andersen et al., 1999)
Copepod (*Eurytemora affinis*)	23	10 day survival nauplii	(Forget-Leray et al., 2005)
copepod (*Tigriopus japonicus*)	Long-term exposure to 0.1, 1.0 and 10 µg/L	F_0 delayed completion of the naupliar stages	(Marcial and Snell, as reviewed by (Crain et al., 2007)
	Long-term exposure to 0.01 µg/L and above	F_1 delayed completion of the naupliar stages	
Aquatic insect (*Chironomus tentans)*	8	↑ HSP and HGB gene expression	(Lee et al., 2006)
periphyton	46	biomass AuC EC50	(Licht et al., 2004)
t1/2 in artificial stream	1 day		(Licht et al., 2004)
Algae	1170 µg/L	96-hr NOEC	Staples (1998)
Daphnia	>3146 µg/L	21 day NOEC	
Daphnia	3900 - 20000 µg/L	48-hr LC50	
Marine Algae	1100 µg/L	96-hr EC50	
Mysid	1100 µg/L	96-hr LC50	
Fish	4600 - 15000 µg/L	48-96-hr LC50	