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Review

Human exposure to bisphenol A (BPA)☆

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Abstract

The plastic monomer and plasticizer bisphenol A (BPA) is one of the highest volume chemicals produced worldwide. BPA is used in the production of polycarbonate plastics and epoxy resins used in many consumer products. Here, we have outlined studies that address the levels of BPA in human tissues and fluids. We have reviewed the few epidemiological studies available that explore biological markers of BPA exposure and human health outcomes. We have examined several studies of levels of BPA released from consumer products as well as the levels measured in wastewater, drinking water, air and dust. Lastly, we have reviewed acute metabolic studies and the information available about BPA metabolism in animal models. The reported levels of BPA in human fluids are higher than the BPA concentrations reported to stimulate molecular endpoints *in vitro* and appear to be within an order of magnitude of the levels needed to induce effects in animal models.

Keywords: Serum; Urine; Epidemiology; Disease; Epoxy resins; Dental sealants; Polycarbonate plastic; Metabolism

Contents

Abbreviations: BADGE, bisphenol A diglycidyl ether; Bis-DMA, bisphenol A dimethylacrylate; BPA, bisphenol A; BPA-gluc, bisphenol A glucuronide; °C, degree Celsius; CDC, Center for Disease Control and Prevention; DHEAS, dehydroepiandrosterone sulfate; DIB-Cl, fluorescent labeling agent, 4-(4,5-diphenyl-1H-imidazol-2-yl)benzoyl chlorine; E, estrogen; ELISA, enzyme-linked immunosorbent assay; ED or ECD, electrochemical detection; ER, estrogen receptor; ESI, electrospray ionization; FD, fluorescence detection; FSH, follicle stimulating hormone; g, grams; GC, gas chromatography; HPLC, high performance liquid chromatography; HRGC, high resolution gas chromatography; i.p., intraperitoneal; i.v., intravenous; IVF, *in vitro* fertilization; kg, kilogram; l, liter; LC, liquid chromatography; LH, lutenizing hormone; LOD, limit of detection; m, meter; mg, milligram; ml, milliliter; MS, mass spectrometry; MS/MS, tandem mass spectrometry; NCI, negative chemical ionization; ND, not detected; ng, nanograms; NIEHS, National Institute for Environmental Health Sciences; NMR, Nuclear Magnetic Resonance; NOAEL, No observable adverse effect level; PCOS, polycystic ovarian syndrome; pg, picograms; pM, picomolar; RfD, reference dose; SPE, solid-phase extraction; subcut, subcutaneous; T, testosterone; TEGDMA, triethylene glycol dimethacrylate; Uncon, unconjugated; UV, ultraviolet

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1. Introduction

The plastic monomer and plasticizer bisphenol A (BPA) is one of the highest volume chemicals produced worldwide, with over six billion pounds produced each year [1]. BPA is used in the production of polycarbonate plastics, epoxy resins used to line metal cans, and in many plastic consumer products including toys, water pipes, drinking containers, eyeglass lenses, sports safety equipment, dental monomers, medical equipment and tubing, and consumer electronics [2]. BPA has been shown to leach from food and beverage containers, and some dental sealants and composites under normal conditions of use. Studies have also determined that BPA can be measured in humans in serum, urine, amniotic fluid, follicular fluid, placental tissue, and umbilical cord blood. In some cases, the levels of total BPA (free and conjugated) in human blood and other fluids are higher than the concentrations that have been reported to stimulate a number of molecular endpoints in cell culture *in vitro* [3], and appear to be within an order of magnitude of the levels of BPA in animal studies [4]; both of these literatures are reviewed in the papers of other panels of this meeting.

Biochemical assays have examined the kinetics of BPA binding to estrogen receptors (ER) and have determined that BPA binds both ERα and ERβ, with approximately 10-fold higher affinity to ERβ [5–7]. The affinity of BPA for ERs is 10,000–100,000-fold weaker than that of estradiol. Until recently, BPA had been considered to be a very weak environmental estrogen because of its low ER affinity and because in many bioassays (e.g., the rodent uterotrophic assay and some responses in human breast cancer cells), BPA can be 10,000–100,000-fold less potent than estradiol. However, results from recent studies of molecular mechanisms of BPA action have revealed a variety of pathways through which BPA can stimulate cellular responses at very low concentrations (reviewed in [8]) in addition to effects initiated by binding of BPA to the classical nuclear or genomic estrogen receptors. Recent findings show that in a variety of tissues, BPA not only has the efficacy of estradiol but is also equally potent, with changes in cell function being observed at a dose of 1 pM (0.23 pg/ml culture medium), through mechanisms that are thought to be non-genomic and involve membrane-associated forms of the estrogen receptors (reviewed in [3]).

"Low-doses" of endocrine disrupting chemicals were defined by the NIEHS Low Dose Peer Review as doses below the accepted NOAEL for the chemical [9], which, for BPA, are doses below 50 mg/kg body weight/day. Initial reports of

adverse effects of BPA at "low-doses" in animal models were below the reference dose (RfD), calculated as an acceptable daily human intake typically 1000-fold below the NOAEL. There are now over 150 published studies describing low-dose BPA effects in animals, including prostate weight and cancer, mammary gland organization and cancer, protein induction in the uterus, organization of sexually dimorphic circuits in the hypothalamus, onset of estrus cyclicity and earlier puberty, body weight, genital malformations and others (reviewed in [4]); over 40 of these are below the RfD for BPA of 50 μg/kg/day. Many of these endpoints are in areas of current concern for human epidemiological trends.

Because of its wide availability in the environment, and its estrogenic activity in specific responses *in vitro* and *in vivo*, adverse effects of BPA exposure on human health are possible [10–13]. It has been hypothesized that exposure during early development to xenoestrogens such as BPA may be the underlying cause of the increased incidence of infertility, genital tract abnormalities, and breast cancer observed in European and US human populations over the last 50 years [14–16].

Here, we have outlined a number of studies that address the levels of BPA in human tissues and fluids. We have also reviewed the few epidemiological studies available that explore the relationship between biological markers of BPA exposure with human health outcomes. We have provided information from several studies that examine the levels of BPA released from consumer products as well as the levels measured in wastewater, drinking water, air and dust. Human exposures are most likely through the oral route, although transdermal exposure by bathing in BPA-contaminated water is also a possible route, as is exposure via inhalation; both of these latter routes of exposure would not be subjected to the extensive first-pass conjugation that occurs with oral ingestion. And finally, we have included several acute metabolic studies that have been performed, along with information available about BPA metabolism in animal models. While this review is by no means comprehensive, we have covered most of the studies that are frequently referenced in the extensive BPA literature.

2. BPA levels in human tissues and fluids

BPA levels have been measured in human fluids and tissues in many developed countries of the world. A general consensus has been accepted that BPA can be detected in the majority of individuals in these countries. The levels of BPA in residents of less-developed countries, however, remain unknown.

2.1. Serum, blood and plasma

Since 1999 [17], more than a dozen studies using a variety of different analytical techniques have measured unconjugated BPA concentrations in human serum (Table 1) at levels ranging from 0.2 to 20 ng/ml serum and exceeding 100 ng/g in one study of placental tissue. These studies have examined blood from both men and women from several countries and at different ages. The techniques used to measure BPA in human serum have included gas chromatography–mass spectrometry (GC–MS), high-performance liquid chromatography (HPLC), derivatization with different chemical agents followed by GC, and ELISA, all with sensitivities for BPA (in serum) ranging from 0.01 to 0.5 ng/ml. Among all of these analytical techniques, MS, specifically isotope dilution-MS, is considered the most accurate and precise method for measuring trace levels of BPA and other environmental chemicals in biological samples. Some researchers suggest that ELISA is not suitable for the measurement of BPA in human samples [18] because this method lacks sensitivity and has many potential confounders in biological matrices. This method was used in seven of the studies listed in Table 1; ELISA and the other techniques detected BPA at similar levels in human serum (Table 1).

BPA determination in human serum requires selective and sensitive methods with limits of detection (LODs) of less than 1 ng/ml because (1) the circulating levels of unconjugated, biologically active BPA in blood of animals following acute low-dose exposures fall in the low picogram to low nanogram per milliliter range [19], and (2) BPA action in cell cultures have been reported in the low picogram to low nanogram per milliliter range (see [3,8] for review). Several older studies were unable to detect BPA in human serum samples. However, these studies used assays with less sensitive methods of detection than modern techniques [20], and thus were unable to detect levels in the nanogram per milliliter range.

Of particular concern are the relatively high levels of BPA measured in many studies in fetal cord serum, maternal serum during pregnancy, and fetal amniotic fluid at developmental stages of perhaps greatest sensitivity to BPA. Several studies have examined BPA levels in serum from pregnant women, umbilical cord blood, and fetal plasma [21–24]. The results from these studies (Table 1) indicate that BPA crosses the maternal-fetal placental barrier. In one report [21], the human maternal sera showed average BPA at 1.4–2.4 ng/ml concentrations, whereas the 15–18-week fetal amniotic fluid showed higher levels averaging 8.3 ng/ml.

Serum BPA concentrations, detected using ELISA, were significantly higher in 11 healthy men compared to 14 healthy women [25]. Additionally, results from this study and another from the same group [26] suggested a significant increase in serum BPA levels from 16 women with polycystic ovarian syndrome (PCOS). Because women with PCOS have higher testosterone levels than healthy women, these studies may suggest that differences in BPA metabolism are related to androgen levels; this was also shown in a study with rats by these authors [27]. However, the implications of the human studies are limited by their small sample sizes.

2.2. Pregnancy-associated fluids

Several investigators have measured BPA levels in placental tissue and amniotic fluid [21–23,28] (see Table 1). In one study, BPA levels in amniotic fluid reached 8.3 ng/ml at 15–18 weeks of gestation, but levels dropped to an average of 1.1 ng/ml in late gestation [21]. The authors of this study proposed that BPA may accumulate in early fetuses due to a lower metabolic clearance of

Table 1
BPA levels in human serum and tissues

Authors	Year	Detection method	Sensitivity (ng/ml)	Endpoint(s)	Levels found [ng/ml (ppb), mean ± S.E.M.]	Unit if not ng/ml	nM equivalence	Other chemicals examined
Sajiki et al. [17]	1999	Electrochemical detection	0.2	Healthy human serum	0–1.6		0–7.0	
		MS/ESI	0.1					
Fung et al. [69]	2000	HPLC/FD	5	Blood collected before and after dental sealant application	Not detected			
Inoue et al. [20]	2000	HPLC with electrochemical detection Coulometric array	0.01 in solvent 0.05 in serum	Healthy human serum	0.32		1.4	
Inoue et al. [115]	2001	LC–MS	0.1	Human plasma or serum	ND – 1.0		ND – 4.4	BADGE
Ikezuki et al. [21]	2002	ELISA	0.3 in serum	Female non-pregnant serum	2.0 ± 0.146		8.8 ± 0.64	
				Early pregnancy serum	1.5 ± 0.197		6.6 ± 0.86	
				Late pregnancy serum	1.4 ± 0.148		6.1 ± 0.65	
				Fetal (cord) serum	2.2 ± 0.318		9.6 ± 1.4	
				Amniotic fluid (15–18 weeks)	8.3 ± 1.573		36.4 ± 6.9	
				Late amniotic fluid	1.1 ± 0.162		4.8 ± 0.71	
				Follicular fluid	2.4 ± 0.133		10.5 ± 0.58	
Schonfelder et al. [22]	2002	Derivatization – GC/MS	0.01 in serum	Fetal (cord) serum	2.9 ± 0.411		12.7 ± 1.8	
				Maternal serum	4.4 ± 0.641		19.3 ± 2.8	
				Placenta	11.2 ± 1.512	ng/g tissue		
Takeuchi and Tsutsumi [25]	2002	ELISA	0.3 in serum	Normal male serum	1.49 ± 0.11		6.5 ± 0.48	Total and free T, E, andostenedione, DHEAS, LH, FSH, prolactin
				PCOS female serum	1.04 ± 0.1		4.6 ± 0.44	
				Normal female serum	0.64 ± 0.1		2.8 ± 0.44	
Tokada and Mori [116]	2002	GC–MS	?	Umbilical cords at birth	Mean, 4.4 ± 1.5; range, 0.11–15.2	ng/g tissue		
Yamada et al. [23]	2002	ELISA	0.5	Normal maternal serum	2.24 (median)		10.5	
				Normal fetal amniotic fluid	0.26 (median)		1.14	
				Abnormal fetal karyotype maternal serum	2.97 (median)		13.0	
				Abnormal fetal karyotype fetal amniotic fluid	0 (median)		0	

Kuroda et al. [117]	2003	HPLC fluorescence derivation, column switching	0.04	Maternal serum	0.46 ± 0.067		2.0 ± 0.29	
				Fetal cord serum	0.62 ± 0.043		2.7 ± 0.19	
				Sterility female serum	0.46 ± 0.044		2.0 ± 0.19	
				Ascitic (peritoneal) fluid	0.56 ± 0.041		2.5 ± 0.18	
Otaka et al. [118]	2003	SPE–GC–MS	0.09	Breast milk	Range 0.65–0.70	ng/g milk		Nonylphenol
Tan and Ali Mohd [24]	2003	GC–MS	0.05	Fetal cord plasma	ND – 4.05 (88% with positive detection)		ND – 17.8	Nonylphenol pesticides, other alkylphenols
Hiroi et al. [119]	2004	ELISA	0.5	Serum from healthy control women, normal endometrium	2.5 ± 0.452		11.0 ± 2.0	
				Serum from women with simple endometrial hyperplasia, benign	2.9 ± 0.632		12.7 ± 2.8	
				Serum from women with complex endometrial hyperplasia, malignant potential	1.4 ± 0.133		6.1 ± 0.58	
				Serum from women with postmenopausal endometrial cancer	1.4 ± 0.189		6.1 ± 0.83	
Sun et al. [29]	2004	DIB-Cl derivatization/HPLC	0.11	Breast milk	0.61 ± 0.042		2.7 ± 0.18	
Takeuchi et al. [26]	2004	ELISA	0.3 in serum	Serum-non-obese normal	0.71 ± 0.09		3.1 ± 0.39	Total and free T, DHEAS, androstenedione
				Serum-non-obese PCOS	1.05 ± 0.10		4.6 ± 0.44	
				Serum-obese normal	1.04 ± 0.09		4.6 ± 0.39	
				Serum-obese PCOS	1.17 ± 0.16		5.1 ± 0.70	
Sugiura-Ogasawara et al. [44]	2005	ELISA	0.5	Serum-control healthy women	0.77 ± 0.067		3.4 ± 0.29	Antinuclear antibodies, prolactin, progesterone, TSH, T4
				Serum-women with recurrent miscarriage	2.59 ± 0.780		11.4 ± 3.4	
Volkel et al. [105]	2005	LC–MS/MS	1.14	Healthy human plasma	Not detected			
Engel et al. [28]	2006	HPLC/electrochemical detection	0.5	Residual amniotic fluid from amniocentesis, <20-week gestation	0.55 (10% > 0.5 ng/ml)		2.41	Enterolactone, daidzein and genistein
Joskow et al. [72]	2006	GC–MS (+ glucuronidase treatment)	0.1	Saliva prior to dental sealant application	0.30 ± 0.043		1.32 ± 0.19	
				Saliva immediately after Delton sealant application	42.8 ± 10.22		187.7 ± 44.8	
				Saliva 1 h after Delton sealant application	7.86 ± 4.24		34.5 ± 18.6	
				Saliva immediately after Helioseal sealant application	0.54 ± 0.20		2.4 ± 0.88	
				Saliva 1 h after Helioseal sealant application	0.21 ± 0.013		0.92 ± 0.06	
Ye et al. [30]	2006	Online SPE–HPLC–MS/MS	0.28	Breast milk	Mean, 1.9; range, ND – 7.3		8.3, range ND – 32.0	Octylphenol, OPP, dichlorophenol, trichlorophenol, BP-3
Kuruto-Niwa et al. [31]	2007	ELISA	0.3	Human colostrum	3.41 ± 0.013		15.0 ± 0.06	

BPA. It was also postulated that the lower level in late gestation was due to the fetus swallowing large amounts of amniotic fluid, allowing BPA to be converted to BPA conjugates by the fetal liver. However, evidence for these hypotheses is still lacking and another study [23] found amniotic fluid concentrations to be lower than maternal serum.

Additional measurements indicate that average levels of BPA in placental tissue were 11.2 ng/g tissue, with an upper range of 104.9 ng/g [22]. Together with the measurements collected in fetal serum, these experiments indicate that the human fetus is likely to be exposed to BPA throughout fetal development, and may be exposed to levels that are even higher than those measured in adult blood.

2.3. Breast milk

An additional and important consideration for the health of the developing neonate is potential BPA exposure from breast milk (Table 1). Because BPA is a somewhat lipophilic compound, it may partition into fat and breast milk. Using HPLC with fluorescence detection, Sun et al. [29] found BPA in the breast milk of all 23 healthy women they examined, at a range of 0.28–0.97 ng/ml and a mean concentration of 0.61 ng/ml [29]. In a study of a similar size ($n = 20$), using HPLC coupled with isotope-dilution tandem MS, Ye et al. [30] detected free BPA in 60% of samples at median concentrations of 0.4 ng/ml and total BPA (free BPA plus BPA conjugates) in 90% of samples, with a median level of 1.1 ng/ml.

Another study of interest reported BPA concentrations in human colostrum, breast milk produced within the first 3 days after giving birth [31,32]. Colostrum is only produced in small quantities, but it has high levels of antibodies, carbohydrates and protein, and low levels of fat. This study examined 101 samples, detecting BPA at a range of 1–7 ng/ml and a mean level of 3.41 ng/ml. It is uncertain if this higher concentration in colostrum compared to breast milk collected more than 1 week after delivery is due to differences in the detection method (HPLC-FD versus ELISA), or whether there are changes in BPA metabolism during the period of lactation.

2.4. Urine

BPA has been measured in human urine from several populations around the world (Table 2). These studies confirm widespread human exposure to BPA, as suspected from the studies of BPA in blood. Most BPA in urine is in its conjugated form, i.e. BPA–glucuronide or BPA–sulfate. Therefore, most researchers use enzymatic (e.g. glucuronidase and/or sulfatase) treatments to measure total (free/unconjugated plus conjugated) BPA in urine. Many also test untreated urine to determine levels of free BPA alone.

The recent study conducted by the US Center for Disease Control and Prevention (CDC) detected BPA in 95% of urine samples from a reference population of 394 American adults using isotope dilution GC–MS [33]. This study reported average levels of total BPA in male and female urine of 1.63 and 1.12 ng/ml, respectively. (These values were corrected for creatine levels to account for different urine volumes produced by individuals, but are not presented here.) It is not unexpected that the range, median and mean for BPA levels reported in this study were very similar to the levels reported in human blood (see Table 1). Similar results were also obtained in a study of 90 young girls; BPA was detected in 94% of samples [34].

Another study also examined sex differences in urinary BPA levels in 30 Korean adults by HPLC with fluorescence detection [35]. This study found no sex differences in total BPA measures (average in 15 men and 15 women, 2.82 and 2.76 ng/ml, respectively). Interestingly, however, men had significantly higher levels of BPA–glucuronide (2.34 ng/ml versus 1.00 ng/ml) while women had significantly higher levels of BPA–sulfate (1.20 ng/ml versus 0.49 ng/ml).

Using pharmacokinetics, urinary BPA levels were extrapolated to estimate daily intake levels. A few studies have used BPA measurements in urine to estimate current levels of exposure; Ouichi and Watanabe [36], using early morning urine samples collected from 48 women and analyzed by HPLC coupled with coulometric electrochemical detection, estimated current intake at 0.6–71.4 μg/day. Additionally, Matsumoto et al. [37] postulated that Japanese University students (50 in 1992 and 56 in 1999) may be exposed to levels of BPA resulting in 10 μg/g creatine from canned coffee and tea. This study estimates that these canned beverages may be a significant source of BPA exposure. The findings from this study also suggested that exposure levels may be decreasing, perhaps due to recent changes in the canning process. While these values are only estimations of current exposure levels, they provide useful data for human risk assessments.

2.5. Semen and follicular fluid

A limited number of studies have examined BPA levels in other bodily fluids such as follicular fluid [21] and semen [38,39]. BPA levels measured in follicular fluid by ELISA showed an average of 2.0 ng/ml [21]. However, because these measurements were made in follicular fluid of women undergoing *in vitro* fertilization (IVF) procedures and this was not a sampling of the general population, it is unknown if the level of BPA detected in follicular fluid during IVF is a valid biomarker or plays a causal role in female fertility. Nevertheless, the detection of BPA in human follicular fluid is of particular concern because of the report that orally administered low-dose BPA in adult mice causes congression failure and aneuploidy in oocytes [40].

BPA levels were also examined in human semen. One study used both an ELISA detection system and HPLC–MS (LODs: 2.0 and 0.5 ng/ml, respectively) to quantify BPA levels in 41 semen samples [38]. While the ELISA detected an average BPA concentration of 5.1 ng/ml, the LC–MS method failed to confirm BPA in any sample. The authors suggest that the ELISA results were inaccurate due to non-specific interactions with BPA-antibodies [38]. In another study, Katayama et al. collected semen samples from 57 men participating in an IVF clinic. BPA was not detected in any of the samples using a proteinase K digestion followed by HPLC with capillary electrophoresis (LOD: 1 pg/ml) [39]. Therefore, it appears unlikely that BPA is present in human semen samples considering the high sensitivities of the assays used.

Table 2
BPA levels in human urine

Authors	Year	Detection method	Sensitivity (ng/ml)	Subjects	Glucuronidase/ sulfatase treatment?	Detection rate	Levels found [ng/ml (ppb), mean ± S.E.M.]				Unit if not ng/ml	Estimated daily intake	Other chemicals examined
							Unconjugated BPA	BPA–glucuronide	BPA–sulfate	Total BPA			
Brock et al. [120]	2001	GC–MS	0.12	Five specimen pools from at least five people	Glucuronidase	5/5 pools	Below level of detection			Range 0.11–.51			
Ouchi and Watanabe [36]	2002	HPLC–ECD with column switching	0.2	Morning samples from 48 women students	Glucuronidase	1/48 (free BPA); 100% BPA–glucuronide	Range ND – 0.2	Range 0.2–9.1				0.6–1.4 μg/day	
Kim et al. [35]	2003	RP-HPLC/FD	0.28	Fifteen male Korean volunteers	Glucuronidase and sulfatase		0.58 ± 0.14	2.34 ± 0.85	0.49 ± 0.27	2.82 ± 0.73			
				Fifteen female Korean volunteers			0.56 ± 0.10	1.00 ± 0.34	1.20 ± 0.32	2.76 ± 0.54			
Matsumoto et al. [37]	2003	HPLC	1.7	Fifty university students in 1992	Glucuronidase and sulfatase	82% detection						10 μg/g creatine	
				Fifty-six university students in 1999		61% detection							
Tsukioka et al. [121]	2003	NCI-GC/MS	0.1	Six urine samples	Glucuronidase	100% detection				Range 0.2–0.8, mean 1.6			
Yang et al. [106]	2003	HPLC/FD	0.012	Seventy-three Koreans with various SULT1A1 polymorphisms	Glucuronidase	75% detection				Range 0.68–86.14, mean ∼ 9.5			
Calafat et al. [33]	2005	GC–MS	0.1	Reference population – 184 American males	Glucuronidase	96% detection				1.63	(μg/g creatinine)		4-Nonylphenol
				Reference population – 210 American females		94% detection				1.12	(μg/g creatinine)		
Liu et al. [122]	2005	HPLC with ECD	0.5	Nine girls	Glucuronidase	89% detection				Range 0.04–6.6, median 2.4			Daidzein, genistein and enterolactone
				Twenty-four adults		52% detection				Range ND – 2.24, median 0.47			
Volkel et al. [105]	2005	HPLC–MS/MS	1.14	Six subjects orally administered 25 μg BPA	Glucuronidase	2/6 samples	Below LOD	Below LOQ					
Ye et al. [123]	2005	Online SPE–HPLC–MS/MS	0.3	Thirty demographically diverse volunteers	Glucuronidase and sulfatase	97% detection	Range ND – 0.6, mean below LOD	Range ND – 19.0, mean 3.1	Range ND – 1.8, mean 0.5	Range ND – 19.8, mean 3.2			
Joskow et al. [72]	2006	GC–MS	0.1	Urine prior to dental sealant application – 14 men	Glucuronidase					2.41 ± 0.33			
				Urine immediately after Delton sealant application	Glucuronidase					27.3 ± 13.03			
				Urine 1 h after Delton sealant application	Glucuronidase					7.34 ± 1.44			
				Urine immediately after Helioseal sealant application	Glucuronidase					7.26 ± 6.04			
				Urine 1 h after Helioseal sealant application	Glucuronidase					2.06 ± 0.47			
Yang et al. [45]	2006	HPLC/FD	0.026	One hundred seventy-two Koreans with various SULT1A1 polymorphisms	Glucuronidase	97.5% detection				Range 0.03–2.4, median 7.86			
Wolff et al. [34]	2007	HPLC–MS/MS	0.36	Ninety young girls, aged 6–9 years	Glucuronidase	94% detection				Range ND – 54.3, mean 2.0			Phytoestrogens, pthalates and eight other phenols

Table 3
Summary of epidemiology studies

Authors	Year	Study type	Measurement of BPA	Health related outcome	Relationship between BPA and disease	Limitations
Hanaoka et al. [43]	2002	Cross-sectional: 82 subjects (42 epoxy resin sprayers and 42 unexposed to BADGE)	Urinary BPA levels (by HPLC) in workers applying epoxy resins and unexposed workers	FSH levels	High BPA levels are associated with lower FSH levels	Confounding exposures (organic solvents) present
Takeuchi and Tsutsumi [25]	2002	Cross-sectional: 14 healthy women, 16 women with PCOS and 11 healthy men	Serum BPA levels (by ELISA)	PCOS	PCOS women had significantly higher BPA than normal women. BPA positively correlated with testosterone among men and women.	Small sample size, cross-sectional design
Yamada et al. [23]	2002	Case control: 48 cases with abnormal karyotype, 200 controls (20 per year) selected from women carrying fetuses with normal karyotypes	BPA levels in maternal serum and amniotic fluid at time of amniocentesis (by ELISA)	Fetus with abnormal karyotype	Higher maternal serum BPA levels in cases with abnormal karyotype as compared to women with fetuses with normal karyotype	Confounders not adjusted for, decline in BPA concentration over 10-year period, a trend also not adjusted for
Kuroda et al. [117]	2003	Cross-sectional: 9 healthy pregnant women, 21 women with sterility	BPA levels in serum and cord blood from pregnant women; serum and peritoneal fluid from women with sterility (measured by HPLC)	Sterility	No difference in serum BPA levels between pregnant and sterile women	Small sample size
Wilson et al. [41]	2003	Observational: 9 pre-school aged children monitored for 48 h	Urinary BPA levels, BPA levels in environmental samples		Primary route of BPA exposure was dietary	Small sample size
Hiroi et al. [119]	2004	Cross-sectional: 7 women with endometrial carcinoma, 9 women with complex endometrial hyperplasia, 10 women with simple endometrial hyperplasia, 11 controls	Serum BPA levels (by ELISA)	Endometrial carcinoma and hyperplasia	BPA lower in complex endometrial hyperplasia and endometrial cancer groups compared to control and simple endometrial hyperplasia groups	No confounders adjusted for, small sample size
Takeuchi et al. [26]	2004	Cross-sectional: 7 cases with hyperprolactinemia, 21 cases of hypothalamic amenorrhea, 13 non-obese PCOS, 19 non-obese controls, 7 obese controls	Serum BPA levels (by ELISA)	Obesity and PCOS	Compared to normal, non-obese women, BPA was higher in obese normal women, obese and non-obese women with PCOS	Small sample size, cross-sectional design
Sugiura-Ogasawara et al. [44]	2005	Cross-sectional: 45 women with recurrent miscarriage and 32 nulliparous women	Serum BPA levels (by ELISA)	Recurrent miscarriage	Mean BPA levels among women with recurrent miscarriage was higher than nulliparous women	Timing of exposure relative to outcome determination, BPA distribution highly skewed, medians identical
Wilson et al. [42]	2006	Observational: 257 preschool children	Urinary BPA levels, BPA levels in environmental samples		Primary route of BPA exposure was dietary	
Yang et al. [45]	2006	Cross-sectional: 68 adults appearing for regular check-up	Urinary BPA (HPLC)	Sister chromatid exchange in peripheral lymphocytes (untreated and MNNG-treated at 0.2 mM, 0.4 mM or 0.6 mM); self-reported reproductive history and symptoms	Urinary BPA positively associated with SCE in untreated and MNNG-treated at 0.2 mM, no association with SCE for MNNG-treated at higher doses, no association between BPA and self-reported reproductive history or symptoms	

3. Epidemiology studies of human exposures

At this time, only a few epidemiological studies have been conducted to investigate the relationship between health-related endpoints and BPA exposure (Table 3). Several human studies have focused on identifying sources or levels of BPA exposure. It is clear that additional epidemiological studies are needed to establish relationships between BPA exposure and health outcomes, especially considering the extensive literature that now exist for adverse effects on animals following exposure to low doses of BPA.

3.1. Sources and estimates of BPA exposure

Two studies have been conducted to estimate BPA exposure levels in young children. The first involved just nine children and was designed to examine their potential exposures at home and in daycare [41]. BPA was detected in indoor and outdoor air samples, floor dust and play area soil in both locations at similar levels. BPA was also detected in liquid and solid food at daycare and at home. Based on these environmental levels, the authors estimated that the average BPA exposure level for young children is 42.98 ng/kg/day. A second observational study performed by the same group of investigators examined BPA exposures in 257 preschool children [42]. This study verified that BPA could be found in more than 50% of indoor air, hand wipe, solid food and liquid food samples. This study's results suggested that 99% of exposures of preschool children originated in the diet; the estimated exposure from dietary sources was 52–74 ng/kg/day, and estimated inhalation exposure was 0.24–0.41 ng/kg/day.

In another study of interest, BPA was measured in the urine of male workers who apply epoxy resins containing bisphenol A diglycidyl ether (BADGE) [43]. Urinary BPA levels were significantly higher in 42 men exposed occupationally than in 42 non-exposed workers.

3.2. BPA exposure and human health effects

As stated above, human studies of possible health effects of BPA exposure are extremely limited. BPA levels in blood have been associated with a variety of conditions in women including obesity, endometrial hyperplasia, recurrent miscarriages, abnormal karyotypes and polycystic ovarian syndrome. Two studies found that women with PCOS had higher serum levels of BPA than women without PCOS and that levels of BPA were positively correlated with circulating androgen levels [25,26]. A negative correlation between BPA and FSH was found among men in the study of epoxy resin workers described above [43] however, the epoxy resin workers were also exposed to organic solvents. Due to the cross-sectional design of these studies, it cannot be determined whether BPA increases androgen levels or if androgen levels affect metabolism of BPA. Three studies found higher BPA exposure for health-related outcomes that are associated with chromosomal abnormalities. One study found higher maternal serum BPA among women carrying fetuses with an abnormal karyotype compared to women carrying fetuses with a normal karyotype [23]. Maternal age, an important potential confounder was not controlled in this study. In another epidemiology study, an association between serum BPA levels and recurrent miscarriage was reported [44]; mean BPA levels were more than three times as high in 45 women with a history of three or more consecutive first-trimester miscarriages compared to 32 non-parous women without fertility problems. Additionally, among 35 women that then became pregnant, there was some evidence of lower BPA among the women who subsequently had a successful pregnancy as compared to those that miscarried again. However, it is important to note that the distribution of exposure among the women with recurrent miscarriage was highly skewed with only a few women with high exposure levels and that the median exposure levels were identical in the two groups. Finally, sister chromatid exchange measured in peripheral lymphocytes was positively associated with urinary BPA levels in adults [45].

Although providing interesting preliminary data on potential health risks, these epidemiology studies have several limitations. Overall, the studies have small sample sizes, limited details on subject selection criteria, and they generally are cross-sectional designs that include limited control for potential confounders. These limitations in design contribute to the limited ability to make conclusions based on the epidemiology of potential health risks of BPA. Finally, due to their design, it was not possible to determine whether altered BPA metabolism is a secondary effect due to the dysfunctions and conditions examined in these studies.

4. Levels of BPA in the environment

Most studies have focused on the potential for BPA exposure from dietary sources. In fact, a significant number of studies have been dedicated to determining BPA levels in foods, especially foods stored in cans with epoxy resin linings. A few other potential sources of BPA exposure, namely drinking water, air and dust, have received far less attention. While several studies have examined BPA leaching from landfills, additional studies are needed to examine these other potential sources and routes of exposure.

Most of the studies described below conclude with a statement about the low level of BPA leaching from a single studied source. Very few studies have estimated total BPA exposure from multiple sources. Using literature from contamination in the environment (water, air, soil) and food contamination (can surfaces, plastic containers), the daily human intake of BPA was estimated at less than 1 μg/kg body weight/day [46]. Alternatively, the European Commission's Scientific Committee on Food [47] estimated BPA exposure to be 0.48–1.6 μg/kg body weight/day from food sources, while Thompson et al. [48] estimated that New Zealanders consume as much as 4.8 μg/day from dietary sources alone.

4.1. BPA from plastics, baby bottles and other consumer products

In 1993, Krishnan et al. [49] found that autoclaving cell culture media in polycarbonate flasks led to the release of an

Table 4A
Leaching levels from baby bottles, consumer plastics and papers

Authors	Year	Sample	Detection method	Sensitivity	Quantification limit	Endpoint(s)	Levels found in product (μg/g)	Leaching levels (ng/ml)	Unit if not ng/ml
Baby bottles									
Mountfort et al. [124]	1997	Twenty-four polycarbonate baby bottles	HPLC/FD	0.03 μg/g		Infant feed in contact with baby bottles after simulated use		Not detected in any sample, before or after simulated use	
Sun et al. [51]	2000	Two polycarbonate baby bottles	HPLC with chemi-lumi-nes-cence detec-tion	0.38 ng/ml		Water in contact with new bottles for 30 min at 95 °C		Bottle A: 0.59 ± 0.04; Bottle B: 0.75 ± 0.045	
						Second test of water in contact with bottles for 30 min at 95 °C		Bottle A: 0.13 ± 0.005; Bottle B: 0.16 ± 0.01	
						Water in contact with bottles for 30 min at 95 °C after brushing		Bottle A: 0.18 ± 0.01; Bottle B: trace levels	
D'Antuono et al. [125]	2001	Four brands of polycarbonate baby bottles purchased in Argentina	LC–ED	0.2 ng/ml		Distilled water in contact with baby bottle for 30 s at 100 °C		1.2	
Brede et al. [52]	2003	Twelve polycarbonate baby bottles purchased in Norway subjected to simulated use	SPE–GC (veri-fied by MS)	0.1 ng/ml		Water food simulant in contact with new bottles for 1 h at 100 °C		0.23 ± 0.03	
						Food simulant in contact with bottles for 1 h at 100 °C after 51 washes and 13 brushes		8.4 ± 1.2	
						Food simulant in contact with bottles for 1 h at 100 °C after 169 washes and 23 brushes		6.7 ± 1.2	
Wong et al. [50]	2005	Twenty-eight polycarbonate baby bottles purchased in Singapore	HPLC (veri-fied by GC–MS)	3 μg/g		Composition of plastic material from baby bottles	Detected in 19 of 28 samples, mean: 28.1		
				50 ng/in.^{2}		Ten per cent ethanol in contact with bottles for 8 h at 70 °C		ND – 580	ng/in.^{2}
						Corn oil in contact with bottles for 8 h at 100 °C		ND – 2560	ng/in.^{2}
Consumer Plastics and Papers									
Vinggaard et al. [55]	2000	Nine paper towels from recycled paper	GC/FTIR/MS	0.2 mg/kg paper		Paper towel composition	Range 0.55–24.1		
		Eleven paper towels from virgin paper				Paper towel composition	Range ND – 0.12		
Nerin et al. [53]	2003	Plastic commercial containers for microwave	HPLC/FD (verified by GC–MS)	0.04 μg/g	0.1 μg/g	Polycarbonate composition	30		μg/g

Table 4A (*Continued*)

Sajiki et al. [126]	2003	Polycarbonate plastic tubing	LC–MS	0.1 ng/ml	Leaching to seawater at 20 °C/day		1.6	
					Leaching to seawater at 37 °C/day		11	
					Leaching to river water at 20 °C/day		0.2	
					Leaching to river water at 37 °C/day		4.8	
					Leaching to control water at 20 °C/day		0.15	
					Leaching to control water at 37 °C/day		0.8	
Lopez-Cervantes et al. [54]	2003	Five commercially available polyvinyl chloride plastic wraps	HPLC/FD (verified by GC–MS)		Plastic wrap composition	Range ND – 483		μg/g
					Leaching into water after 10 days of exposure at 40 °C		Range ND –11.5	μg/dm^2
					Leaching into 3% acetic acid after 10 days of exposure at 40 °C		Range ND – 11.9	μg/dm^2
					Leaching into olive oil after 10 days of exposure at 40 °C		Range ND – 30.7	μg/dm^2
Ozaki et al. [56]	2004	Sixteen virgin paper products in food contact	GC–MS	0.02 mg/kg paper	Paper composition	Range ND – 0.36, detected in 81.3% of samples		
		Twelve recycled paper products in food contact			Paper composition	Range ND – 26, detected in 66.7% of samples		
Sajiki et al. [127]	2004	Polycarbonate plastic tubing	HPLC		Leaching (per day) to water over several weeks		0.5	
					Leaching (per day) to albumin (50 mg/ml)		3	
Lopez-Espinosa et al. [57]	2007	Thirty-two cardboard samples for take-out food	HPLC (verified by GC–MS)	22.8 ng/ml	Cardboard composition	Range ND – 18.17, detected in 46.9% of samples		
		Eight paper products for take-out food			Paper composition	Range ND – 1.88, detected in 37.5% of samples		

unknown estrogenic substance. Using NMR and mass spectrometry, it was determined that the flasks were leaching BPA. At that time, Krishnan et al. speculated that these results could impact other scientific experiments using media autoclaved in polycarbonate flasks.

Subsequent studies have examined leaching from polycarbonate baby bottles using a variety of methods including HPLC, LC–ED, and GC–MS (Table 4A). BPA leaching has been observed from polycarbonate baby bottles manufactured in many different countries [50]. Different results have been obtained from various groups studying the effects of washing, boiling, and brushing on BPA leaching. Sun et al. [51] found that BPA leached from polycarbonate bottles, but not glass bottles, on their first use. However, during subsequent use, BPA concentrations were below the LOD. Alternatively, Brede et al. found that rounds in a dishwashing machine, boiling water and brushing led to significantly higher concentrations of BPA leaching into water [52]. Based on these measured levels of leaching, average dietary exposure to BPA was estimated for infants from birth through 3 months of age, the period when infants consume exclusively liquid foods [50]; these calculations estimated that newborns, because of their lower body weight, are exposed to the highest levels of BPA (24 μg/kg body weight/day). By 3 months of age, dietary exposure estimates drop to 15 μg/kg body weight/day.

Other polycarbonate containers (e.g., Tupperware) intended to be used as reusable food containers, have the potential to leach BPA. Many of these containers are marketed for use in the microwave, although heating may increase BPA leaching levels. Nerin et al. [53] examined the composition of a microwavable polycarbonate plastic container. BPA was found in the plastic at a concentration of 30 μg/g plastic and the potential migration level was estimated at 6.5 μg/g of food. However, this study only made leaching estimates, and its authors acknowledged that assessments of actual leakage from plastic products are still needed. In another study with potential implications for food safety, BPA levels in plastic stretch film used in food packaging were examined [54]. An examination of five polyvinyl chloride stretch films indicated measurable BPA content in four samples that ranged from 43 to 483 mg/kg film. The migration of BPA from these products was tested into water, acetic acid (3%) and olive oil. Three of five films showed leaching into water and acetic acid, while four of five leached BPA into olive oil, illustrating the potential for BPA contamination of consumer food products.

Chemical analysis has also been performed on some papers and cardboards used as food containers (Table 4A). BPA is often used as a developer in paper production, so its presence in food-contact papers is not unexpected. In an analysis of 20 different brands of kitchen paper towels (also called kitchen rolls), extracts from paper towels made with virgin paper contained no BPA, with the exception of one brand, with 0.12 mg/kg [55]. In contrast, paper towels made from recycled paper had BPA levels ranging from 0.55 to 24.1 mg/kg. In a second study examining 28 paper products in food-contact use, 67% of the 12 products made from recycled paper contained BPA at a range of 0.19–26 mg/kg [56]. Of the 16 products made from virgin paper, 13 contained detectable levels of BPA, albeit at much lower concentrations (range 0.034–0.36 mg/kg). A final study examined BPA levels in paper and cardboard containers used for take-out food [57]. Forty containers were collected in four European countries and the portion of the container in direct contact with food was analyzed. BPA was detected in 45% of the paper samples examined, with higher levels in cardboard than in paper. Collectively, these studies indicate that a wide range of food-contact papers and cardboards serve as potential sources of BPA contamination in foods. However, no studies measured the actual contamination of food items in contact with these papers and cardboards. Additional studies to examine actual leaching rates are still needed.

4.2. Leaching of BPA from food cans and containers

Metallic food cans are protected from rusting and corrosion by the application of epoxy resins as inner coatings. Many of these resins are synthesized by the condensation of BPA with epichlorhydrin to create BADGE [2]. When incomplete polymerization occurs, residual BPA may leach from the epoxy resin and has the potential to contaminate stored foods.

Several studies have documented conditions that support or enhance BPA migration from the coating of cans (Table 4B). These studies have obtained cans from manufacturers and performed carefully controlled studies on the influence of heating time, heating temperature, storage time, storage temperature, and other factors on the level of BPA migration. One of the earliest studies quantified BPA leaching at a range of 4–23 μg of BPA per can [58]. Kang et al. [59] conducted a comprehensive study and found that heating temperature had a significant effect on BPA migration, to a greater extent than heating time. Vegetable oil and sodium chloride solutions were also found to significantly increase BPA leaching. Takao et al. also found an influence of temperature on the release of BPA from coated cans [60]. While low levels of BPA were detected in water stored in unheated cans, when cans were heated to 100 °C, a normal temperature for the preservation of canned foods, the BPA concentrations in the water increased 1.7–55.4 times (mean 18.2×) the unheated concentration.

Many studies have also examined BPA levels leaching from epoxy resins lining cans to specific foods (Table 4C). BPA has been detected in canned pet foods [61], vegetables [58,62,63] and fish [63,64]. Others have found BPA contamination in infant formula [65,66]. Thompson et al. [48] used information available from the literature to estimate total dietary estrogen exposures for New Zealand population subgroups. The available literature led the authors to conclude that BPA accounts for approximately 34% of the estrogenic exposure in the New Zealand diet, with estimated intakes of 4.1–4.8 μg/day.

4.3. Leaching of BPA from dental products

Several resin-based monomers are used in dentistry as preventative sealants, adhesives and restorative materials. Since the 1960's, BPA diglycidyl methacrylate has been used as a component of many dental restorative materials. These monomers are typically polymerized *in situ* to levels of double bond conver-

Table 4B
Leaching levels from cans and epoxy resins

Authors	Year	Sample	Detection method	Sensitivity (ng/ml)	Quantification limit	Endpoint(s)	Leaching levels (ng/ml)	Unit if not ng/ml
Brotons et al. [58]	1995	Cans containing 20 different types of food product	HPLC (verified by MS)			Water autoclaved in cans for 30 min at 125 °C	Range 4–23	μg/can
Bae et al. [128]	2002	Three epoxy resins	GC–FID	2.97	7.7	Resin applied to glass plates and autoclaved in water	Range 0.32–89.79	
Kang et al. [129]	2002	Cans with epoxy resin linings	HPLC/FD			Water sealed into cans, heated for 30 min at 121 °C	Range 7–31	
Takao et al. [60]	2002	Cans with epoxy resin linings	GC–MS	0.05		Water sealed into cans, unheated	Detected in 100% of samples	
						Water sealed into cans, heated for 30 min at 80 °C	1.6–16.7× higher than levels in unheated cans	
						Water sealed into cans, heated for 30 min at 100 °C	1.7–55.4× higher than levels in unheated cans	
Kang et al. [59]	2003	Cans with epoxy resin linings	HPLC	1		Water autoclaved in cans for 30 min at 105 or 121 °C	At 105 °C: 1.0; at 121 °C: 5.0	
						Glucose solution autoclaved in cans for 30 min at 121 °C	Range 7–8	
						Sodium chloride solution autoclaved in cans for 30 min at 121 °C	>10	
						Vegetable oil autoclaved in cans for 30 min at 121 °C	Range 16–18	

Table 4C
Leachates detected in food products

Authors	Year	Sample	Detection method	Sensitivity	Quantification limit (ng/g)	Endpoint(s)	Leaching levels (ng/g)	Units if not ng/g
Brotons et al. [58]	1995	Canned vegetables and fatty foods	HPLC (verified by MS)			Liquid phase of vegetables packed in lacquer-coated cans	Range ND – 22.9	μg/can
Biles et al. [130]	1997	Infant formula	SPE-HPLC/FD (verified by GC–MS)	0.9 ng/ml		Canned infant formula	Range 0.1–13.2	ng/ml
Howe and Borodinsky [131]	1998	Food-simulating solvents	HPLC	1000 ng/g		Food simulants (water, 10% ethanol, 3% acetic acid, coconut oil)	Not detected in any sample	
Yoshida et al. [62]	2001	Canned vegetables and fruit	HPLC/UV	5 ng/g		Solid portion of canned food Aqueous portion of canned food	Range <10.0–95.3 Not detected	
Goodson et al. [63]	2002	Survey of canned foods	GC–MS	2 ng/g	7	Canned vegetables, infant formula, fish, beverages, soup, meat	Detected in 38 of 62 samples	
Kang and Kondo [129]	2002	Canned instant coffee	HPLC/FD	10 ng/ml 2 ng/ml		Decaffeinated instant coffee Non-decaffeinated instant coffee Caffeine solution (0.1 mg/ml) Caffeine solution (1.0 mg/ml)	66.2 ± 5.99 84.0 ± 5.86 23.8 ± 3.90 79.7 ± 5.91	ng/ml ng/ml ng/ml ng/ml
Kang et al. [61]	2002	Canned pet foods	HPLC/FD			Canned cat food Canned dog food	Range 13–136 Range 11–206	
Munguia-Lopez et al. [132]	2002	Cans containing jalapenos and acidic food simulants	HPLC/FD (verified by GC–MS)	2 ng/ml		Canned jalapeno peppers Acid food simulant stored in cans for 4 h at room temperature (25 °C) Acid food stimulant stored in cans for 4 h at 35 °C Acid food simulant stored in cans for 160 days at 25 °C Acid food simulant stored in cans for 160 days at 35 °C	5.59 ± 3.05 Not detected in any sample Not detected in any sample 2.25 ± 0.72 15.33 ± 0.65	
Inoue et al. [109]	2003	Levels in honey	LC–MS	20 ng/ml		One hundred and seven honey samples	Range ND – 33.3	
Kuo et al. [66]	2004	Powdered milk and infant formula	GC–MS		1	Milk and infant formula	Range 45–113	
Munguia-Lopez et al. [64]	2005	Cans containing tuna fish or fatty-food simulant	HPLC (verified by GC–MS)	5 ng/ml		Canned tuna fish Fatty-food simulant stored in cans for 4 h at room temperature (25 °C) Fatty-food simulant stored in cans for 4 h at 35 °C Fatty-food simulant stored in cans for 160 days at 25 °C Fatty-food simulant stored in cans for 160 days at 35 °C	Range <7.1–102.7 Not detected in any sample 646.5 ± 63.4 186.1 ± 18.6 398.7 ± 30.9	
Maragou et al. [133]	2006	Canned milk (whole evaporated, partly skimmed evaporated, powdered infant formula)	SPE with LC–ESI–MS	1.7 ng/g	5 .1	Canned milk	Range <1.7–15.2	

Table 4D
Leaching levels from dental sealants

Authors	Year	Sample	Detection method	Sensitivity (ng/ml)	Quantification limit	Endpoint(s)	Levels found in product (μg/ml)	Leaching levels (μg/ml)	Units if not μg/ml
Olea et al. [67]	1996	Four commercial composite dental resins	HPLC (verified by GC–MS)			Resin composition	At neutral pH, range 0.005–0.677		μg/mg sealant
		Eighteen patients with 50 mg of sealant applied to a total of 12 molars				Saliva 1 h after application		Range 3.3–30	
Nathanson et al. [76]	1997	Seven commercial dental sealants	HPLC (verified by GC–MS)	0.1[a]		Eluates from sealants treated with light *in vitro*	Undetected in any sample		
Arenholt-Bindslev et al. [68]	1999	Eight patients with a total of 38 mg of sealant applied to a total of four molars	HPLC	100	300	Saliva immediately after application		Range ND – 2.8, mean 1.43	
						Saliva 1 h after application		Undetected in any sample	
						Saliva 24 h after application		Undetected in any sample	
Lewis et al. [73]	1999	Twenty-eight commercial composite dental resins	HPLC with infrared analysis			Resin composition	Detected in two products		
Noda et al. [134]	1999	Five dental resin composites	HPLC (verified by UV spectra)			Raw resin composition	0.001–0.0022		μg/mg sealant
Schmalz et al. [74]	1999	Five commercial dental resins	HPLC	200		Eluates from sealants made from BADGE	Range 2–8		
						Eluates from sealants made from bis-GMA	Not detected		
						Eluates from sealants made from bis-DMA	Range 4–155		
Fung et al. [69]	2000	Twenty-two patients with 32 mg of sealants applied to a total of four molars	HPLC/FD	5		Saliva 1–3 h after application		Range 0.0058–0.1056	
Pulgar et al. [75]	2000	Eight dental compounds	HPLC (verified by GC–MS)	200	230	Composition before *in vitro* polymerization	At neutral pH, range ND – 155		
						Composition after *in vitro* polymerization	At neutral pH, range ND – 42.8		
Tarumi et al. [77]	2000	Sixteen commercial dental resins	HPLC (verified by GC–MS)	0.1		Resin composition	Undetected in any sample		
Zafra et al. [70]	2002	Eight patients undergoing dental repairs	GC–MS	3	12	Saliva 1 h after application		Range 0.0153–0.0324	
Al-Hiyasat et al. [135]	2004	Resin based Z-100 dental sealant	HPLC			Eluates from sealant samples after 3 weeks *in vitro*	78		
Wada et al. [78]	2004	Twenty-four commercial dental composites	GC–MS	1		Eluates from composites	Undetected in any sample		
Sasaki et al. [71]	2005	Twenty-one patients treated with one of nine resins	ELISA			Saliva immediately after application		Range 0.0210–0.0601	
						Saliva after application and gargling		Range 0.0016–0.0047	
Joskow et al. [72]	2006	Patients treated with one of two dental sealants	GC–MS	0.1		Saliva prior to dental sealant application		0.00030 ± 0.000043	
						Saliva immediately after Delton sealant application		0.0428 ± 0.01022	
						Saliva 1 h after Delton sealant application		0.00786 ± 0.00424	
						Saliva immediately after Helioseal sealant application		0.00054 ± 0.00020	
						Saliva 1 h after Helioseal sealant application		0.00021 ± 0.000013	

[a] Value in ng/mg

sion that range from 60 to 80%. Small quantities of unreacted monomers have been shown to leach from polymerized dental materials (see Table 4D) and the potential exists for either residual BPA carried over from the manufacture of these monomers or from biological breakdown of the leached monomers to BPA *in vivo*.

In a study of 18 adults, Olea et al. [67] applied approximately 50 mg total of sealant to 12 molars. Total saliva was collected continuously for 1 h before and 1 h after the application procedure. After the treatment, all samples were found to contain variable amounts of BPA, ranging from 3.3 to 30.0 μg/ml saliva. Subsequent studies, using different composite applications and saliva collection techniques, have added some controversy to this topic. Arenholt-Bindslev et al. [68] applied 38 mg of fissure sealant to four molars in eight volunteers and found detectable levels of BPA in small saliva samples taken immediately after placement of the sealant. However, no BPA was detected in samples collected at 1 h or 24 h after sealant application. Fung et al. [69], however, detected BPA in some saliva samples of dental patients collected at 1 and 3 h after the application of dental materials. The number of detectable saliva samples decreased with sealant dose and the time after application. No BPA was detected in saliva samples collected at 1, 3 or 5 days after treatment, and BPA was not detected in any serum specimens collected at the same time as the saliva samples. Zafra et al. [70] collected saliva samples from eight patients undergoing dental procedures and found BPA in all specimens. BPA levels ranged from 15.3 to 32.4 ng/ml. Sasaki et al. [71] used an ELISA method to detect BPA in saliva samples from 21 patients treated with one of nine commercially available dental resins. BPA was detected in saliva at several 10–100 ng/ml following treatment with composite resins; however, gargling was found to remove measurable levels of BPA from subsequent saliva samples.

In a recent study, Joskow et al. [72] examined BPA in urine and saliva of 14 adults treated with one of two different dental sealants. Saliva samples were collected before, immediately after, and 1 h after sealant application. Urine samples were collected before and at 1 and 24 h after sealant placement. The total concentrations of BPA were measured by two different isotope dilution-MS-based techniques. Saliva levels were found to be highest immediately following treatment while the highest mean urinary levels were measured 1 h following sealant application. These highest mean saliva and urine levels were 42.8 and 27.3 ng/ml, respectively, in patients treated with one dental sealant. Levels measured in the saliva and urine of patients treated with the second sealant were 0.54 and 7.26 ng/ml, respectively. These findings indicate that sealants produced by different manufacturers release markedly different amounts of BPA, and further research is needed to identify the sealants that leach the lowest amount of BPA for the shortest periods of time.

Finally, several additional studies have shown significant differences in either the composition or the leaching levels of dental sealants from different manufacturers [68,73–75,71,72] while other studies have been unable to detect BPA in either dental sealants or eluates [76–78]. Additionally, the storage of saliva samples can affect the detection of BPA [79]. Saliva samples were spiked with BPA, BPA dimethylacrylate (bis-DMA), or triethylene glycol dimethacrylate (TEGDMA). The samples were stored at −20 or −70 °C, and then tested by HPLC and GC–MS (LOD: 1 ng/ml). After storage at −20 °C, BPA levels were found to be higher than in the original samples, while bis-DMA levels were decreased, indicating that this conjugate is unstable and may be deconjugated during storage. However, BPA bis-DMA and TEGDMA were all stable in salivary samples stored at −70 °C. These results may affect the interpretation of other studies that used sealant products containing bis-DMA and examined BPA in saliva following sample storage.

4.4. Sewage leachates and water

Several studies have demonstrated that BPA can be detected in landfill leachates (Table 5). Kawagoshi et al. [80] used both chemical analysis (GC–MS) and a yeast two-hybrid system to analyze estrogenic compounds leaching into groundwater from a landfill located in Osaka North Port, Japan. Several xenoestrogens and anti-estrogens were detected, but BPA was identified as the greatest contributor to the measured estrogenic activity, with a contribution ratio estimated at 84% and levels detected at 740 ng/ml. In a study of leachates from a landfill in West Germany, the BPA concentration measured from the raw leachate was 3.61 mg/l [81], in the upper range of levels detected in Japan [82]. While treatment of raw leachates using methods similar to those used to care for landfill waste throughout Europe removed 97% of the estrogenic activity, traces of BPA remained [81]. The authors from these studies suggest that BPA degradation from plastic waste buried in the landfill is the primary contributor to these high levels. These findings contrast with the view of plastic products as primarily posing a problem because of their resistance to degradation in contrast with biodegradable materials. The reality is that the leaching of chemicals such as BPA from plastics in landfills has the potential to contribute to contamination of the environment, particularly because such a large volume is produced annually and such a small proportion is recycled [83].

To assess the potential for BPA to reach drinking water, samples from sewage treatment works effluents, rivers, creeks and drinking water reservoirs were collected in Germany [84]. Using an extraction derivation reaction to convert contaminants into their pentaflouorobenzoylate esters followed by GC–MS, Kuch and Ballschmiter achieved an LOD of 20 pg/l for BPA. BPA was detected in all river samples in concentrations ranging from 500 pg/l to 16 ng/l; BPA levels in drinking water ranged from 300 pg/l to 2 ng/l. BPA was also detected in surface water in 96 samples collected from 38 different locations distributed equally throughout the Netherlands [85]. Twenty percent of samples collected showed detectable levels of BPA (LOD: 11 ng/l) and nine locations had levels over 100 ng/l. Another comprehensive study of wastewater contaminants found that BPA was detectable in 41.2% of 139 streams sampled across 30 US states [86]. This study found a median level of detection of 0.14 μg/l, and a maximum measure of 12 μg/l.

Table 5
Environmental levels of BPA in air, dust and water

Authors	Year	Environmental sample	Detection method	Sensitivity	Quantification limit	Endpoint(s)	Detection rate	Detected levels (ng/l)	Unit if not ng/l
Rudel et al. [136]	1998	Waste water, septage and ground water	HPLC GC/MS	0.0054 μg/l	0.0162 μg/l	Untreated septage	Detected at four of five sites	Range 110–1700	
						Untreated wastewater	Detected at three of four sites	Range 94–150	
						Treated septage and wastewater	100% detection (three sites)	Range 20–55	
Kuch and Ballschmiter [84]	2001	Water	SPE–HRGC-(NCI)–MS	0.04 ng/l		Sewage treatment works effluents	Detected at 15 of 16 sites	Range 4.8–47; mean 16	
						River water in Germany	100% detection (31 sites)	Range 0.5–14; mean 4.7	
						Drinking water	100% detection (10 sites)	Range 0.5–2.0; mean 1.1	
Rudel et al. [89]	2001	Residential air and dust	GC–MS			Indoor air	Detected in three of seven homes/offices and one plastics workplace	Range 2–3 in homes/offices and 208 in plastics workplace	ng/m^3
						Dust samples	Detected in three of six homes/offices	Range 0.25–0.48	μg/g
Yamamoto et al. [82]	2001	Landfill leachates	GC–MS	500 ng/l		Leachates from hazardous waste landfills	Detected at 7 of 10 sites	Range 1.3–17,200,000. median 269,000	
Belfroid et al. [85]	2002	Surface water	GC–MS/MS	11 ng/sample	32 ng/sample	Surface water throughout the Netherlands	20–40% detection, depending on season	Range ND – 21,000	
Kolpin et al. [86]	2002	Surface water	SPE–LC/MS–ESI		90 ng/l	US streams and wastewater	41.2% detection	Median 140	
Zafra et al. [70]	2002	Urban wastewater	GC–MS	0.3 ng/l	0.8 ng/l	Wastewater samples after treatment with disinfection procedures	Not detected in any samples		
Coors et al. [81]	2003	Landfill leachates	GC–MS			Raw landfill leachates		3.61	mg/l
						Treated landfill leachates		46,200	
Kawagoshi et al. [80]	2003	Landfill leachates	GC–MS	500 ng/l		Groundwater outside Japanese landfill		740,000	
Rudel et al. [88]	2003	Indoor air and dust	GC–MS			Indoor air	Not detected in 120 homes	<18	ng/m^3
						House dust samples	Detected in 86% of 118 homes	Range 0.2–17.6; median 0.821	μg/g
Matsumoto et al. [137]	2005	Air particulates	GC–MS	0.01 ng/m^3		Urban ambient outdoor air		Range 0.02–1.92; mean 0.51	ng/m^3

4.5. Air and dust

Air and dust levels of BPA serve as another potential source for human BPA exposure (Table 5). Because of the large amounts of BPA produced annually, it is plausible that BPA enters air particles during production at plastics manufacturing plants. It has been speculated that the presence of BPA in other environmental samples (water, soil, etc.) could lead to its vaporization, despite its low vapor pressure, allowing it to be adsorbed into the core portion of airborne particles [87].

In a survey of 120 homes for the presence of endocrine disrupting chemicals, Rudel et al. [88] found BPA present in 86% of house dust samples at concentrations ranging from 0.2 to 17.6 μg/g. Another study from the same group found BPA in three of six residential and office dust samples [89]. BPA was also detected in air samples, including a sample from a plastics workplace (208 ng/m^3). An additional study measured BPA levels in urban ambient outdoor air particulates in Osaka, Japan [87]. BPA was detected in air samples with an average level of 0.51 ng/m^3. This study also found mild seasonal variation in BPA levels, with increasing levels from autumn to winter and decreasing levels from winter to spring.

5. BPA metabolism in humans and animals

The metabolic elimination pathways for BPA need to be considered for human risk assessment. However, only a limited number of human studies have addressed these issues for several reasons, including ethical considerations and difficulties in identifying individuals that are completely unexposed to BPA from the environment [33,72]. In contrast, many studies have been dedicated to addressing the question of BPA metabolism in animal models, particularly rodents (Table 6). However, a major weakness to current metabolic studies is that, while current evidence indicates that humans are experiencing multiple exposures each day, virtually all of the current metabolic studies are based on kinetics following a single, usually high dose. A clear research need is pharmacokinetic studies that involve multiple exposures to BPA to more accurately reflect typical human exposures as supported by the substantial literature of exposures from multiple sources that have been detailed in prior sections of this review. The conclusion reached by some investigators based on acute metabolic studies is that human exposure should essentially be non-existent [90,91]. However, these conclusions are contradicted by the extensive measurements of parent, unconjugated BPA in blood and tissues at ng/ml levels (see Table 1), which would be impossible according to these conclusions.

With regard to measurable background levels of BPA, there are many other estrogenic environmental contaminants as well as contaminants with other modes of activity that are present in most people examined [33,34]. In addition to BPA, humans are thus exposed to at least dozens of other chemicals that show estrogenic activity, and the likelihood of at least additive effects in humans by other estrogenic endocrine disrupting chemicals is currently not taken into account in regulating human exposure levels to these chemicals.

While oral, dietary exposure is currently considered a major route of human exposure to BPA, the wide range of sources of human exposure detailed in Tables 4 and 5 document the additional importance of exposures that avoid the first-pass hepatic metabolism following oral exposure. Specifically, animal studies involving subcutaneous exposure by injection and by osmotic pump are relevant to human exposures by dermal contact with air, dust and water. Intravenous and intraperitoneal exposure in animals are relevant to inhalation exposure to BPA carried by airborne dust, which has direct access to the systemic circulation. In addition, both of these routes are relevant to human exposures through intravenous medical tubing and exposure to implanted plastics used in surgery.

Another critical issue is that it is well known that the fetus and neonate show very limited first-pass metabolic capability for BPA and other endocrine disruptors [92], and the pharmacokinetics of BPA based on adult oral exposure cannot be used to predict pharmacokinetics in the fetus, neonate or child; the maxim in pediatric medicine that "children are not little adults" is relevant to this issue. Given the ppb levels of parent BPA reported to be present in human blood and tissues, it cannot be assumed that these levels are achieved based only on oral exposure, although this is a major route of exposure. Accounting for all sources of BPA in human blood is an important research need.

5.1. Animal models of BPA pharmacokinetics and relation to circulating levels of free, unconjugated (aglycone), biologically active BPA

The routes by which adult animals are exposed to BPA affect the resulting circulating levels. Studies have used oral gavage, spiked water, intravenous and intraperitoneal injections, slow release capsules, and osmotic pumps, and results of many of these studies are detailed in Table 6, particularly in reference to levels of free, unconjugated BPA in circulation. As noted above, BPA may be absorbed by transdermal exposure by bathing in BPA-contaminated water, or by exposure via inhalation, and both routes avoid the first-pass conjugation that occurs with oral administration. Metabolism of BPA converts a majority of the parent compound to BPA glucuronide(s) and BPA sulfate(s), the levels of which are reported in many studies.

The estrogenic activity of BPA conjugates has been reported as very low to none [93,90,94], and the active molecules are limited to unconjugated aglycones. The possibility that conjugates may be deconjugated locally in tissues to release biologically active BPA is an interesting hypothesis; however, to date there is no published information indicating that this is occurring. Because the parent unconjugated BPA is the only form shown to be biologically active and the published measures of human circulating BPA are solely of the unconjugated, bioactive form (Table 1), this review of the pharmacokinetics of BPA will focus particularly on circulating levels of the parent form in animal studies for comparison to the human circulating BPA levels.

A major portion of the animal literature on low-dose effects has used oral administration of low-dose BPA. This subset of the published animal response studies (reviewed in [4]) will be compared to the adult animal metabolic studies of oral expo-

Table 6
Summary of acute metabolic studies

Authors	Year	Species	Dose administered	Dosing method	Detection method	Sensitivity	Endpoint(s)	Levels found (% of dose administered)				Levels measured (μg/g)			Unconjugated BPA (ng/ml)
								Unconjugated BPA	BPA–glucuronide	BPA–sulfate	Total BPA	BPA conjugated and/or total	Unconjugated BPA	Units if not μg/g	Scaled to oral dose of 50 μg/kg
Miyakoda et al., 1999	1999	Rats (pregnant, gestational day 19)	10 mg/kg	Oral	GC–MS with selective ion monitoring after acetylation	1.5–2 ng/ml plasma	Plasma, 1 h after dosing						34	ng/ml	0.17
							Plasma, 3 h after dosing						*3.6*	ng/ml	0.018
							Plasma, 24 h after dosing						*3.0*	ng/ml	0.015
							Fetus, 1 h after maternal dosing						*11.4*	ng/g	
							Fetus, 3 h after maternal dosing						*4.4*	ng/g	
							Fetus, 24 h after maternal dosing						*7.5*	ng/g	
Miyakoda et al., 2000	2000	Rats (pregnant, gestational day 19)	10 mg/kg	Oral	GC–MS with selective ion monitoring after acetylation	1.5–2 ng/ml plasma	Fetus, 1 h after maternal dosing						*54*	ng/g	
							Fetus, 1 h after maternal dosing, glucuronidase-treated						*54*	ng/g	
		Rats (male)					Plasma, 1 h after dosing					*580*	*62*	ng/ml	0.31
							Plasma, 3 h after dosing					*295*	*23*	ng/ml	0.115
							Plasma, 8 h after dosing					*640*	*12*	ng/ml	0.06
							Testis, 1 h after dosing					*160*	*21*	ng/g	
							Testis, 3 h after dosing					*36*	*22*	ng/g	
							Testis, 8 h after dosing					*36*	*42*	ng/g	
Pottenger et al. [90]	2000	Rats (males)	10 mg/kg	Oral	HPLC w/ GC–MS		Urine collections for 72 h	1.8	9.6	0.48					
							Fecal collections for 72 h	81.29							
		Rats (female)					Urine collections for 72 h	1.5	20.2	0.74					
							Fecal collections for 72 h	71.65							
		Rats (males)		i.p.			Urine collections for 72 h	0.72	8.6	0.49					
							Fecal collections for 72 h	83.17							
		Rats (female)					Urine collections for 72 h	0.9	18.3	0.76					
							Fecal collections for 72 h	64.07							
		Rats (males)		Subcut			Urine collections for 72 h	0.77	9.2	0.59					
							Fecal collections for 72 h	80.19							
		Rats (female)					Urine collections for 72 h	0.93	23.2	1.8					
							Fecal collections for 72 h	54.4							
		Rats (male)	100 mg/kg	Oral		100 ng/g	Blood, 0.083 h after dosing						*0.22*		0.11

Table 6 (*Continued*)

							Blood, 0.25 h after dosing	*0.17*	0.085
							Blood, 0.5 h after dosing	*0.16*	0.08
				i.p.			Blood, 0.5 h after dosing	*8.3*	
							Blood, 2 h after dosing	*2*	
							Blood, 8 h after dosing	*0.56*	
				Subcut			Blood, 0.5 h after dosing	*5.1*	
							Blood, 2 h after dosing	*3.5*	
							Blood, 18 h after dosing	*0.2*	
		Rats (female)		Oral			Blood, 0.5 h after dosing	*1.4*	0.7
							Blood, 2 h after dosing	*0.36*	0.18
							Blood, 12 h after dosing	*0.195*	0.0975
				i.p.			Blood, 0.5 h after dosing	*11*	
							Blood, 2 h after dosing	*1.9*	
							Blood, 24 h after dosing	*0.29*	
				Subcut			Blood, 0.5 h after dosing	*3.9*	
							Blood, 2 h after dosing	*2.8*	
							Blood, 24 h after dosing	*0.25*	
		Rats (male)	10 mg/kg	Oral		10 ng/g	Blood, 0.5 h after dosing	NQ	NQ
							Blood, 2 h after dosing	NQ	NQ
							Blood, 24 h after dosing	NQ	NQ
				i.p.			Blood, 0.5 h after dosing	*0.7*	
							Blood, 2 h after dosing	*0.18*	
							Blood, 4 h after dosing	*0.049*	
				Subcut			Blood, 0.5 h after dosing	*0.3*	
							Blood, 2 h after dosing	*0.33*	
							Blood, 12 h after dosing	*0.038*	
		Rats (female)		oral			Blood, 0.5 h after dosing	*0.022*	0.11
							Blood, 2 h after dosing	*0.016*	0.08
							Blood, 24 h after dosing	*0.011*	0.055
				i.p.			Blood, 0.5 h after dosing	*0.85*	
							Blood, 2 h after dosing	*0.12*	
							Blood, 18 h after dosing	*0.018*	
				Subcut			Blood, 0.5 h after dosing	*0.28*	
							Blood, 2 h after dosing	*0.25*	
							Blood, 24 h after dosing	*0.016*	
Takahashi and Oishi [111]	2000	Rats (pregnant, gestational day 18)	1 g/kg	Oral	HPLC w/ UV detection	5 ng/g	Maternal blood 10 min after dosing	2.89	0.1445
							Maternal blood 20 min after dosing	14.7	0.735
							maternal blood 0.5 h after dosing	*2.0*	0.1
							Maternal blood 2 h after dosing	*1.2*	0.06
							Maternal blood 6 h after treatment	0.29	0.0145
							Maternal blood 24 h after treatment	*0.13*	0.0065
							Maternal blood 48 h after treatment	*0.083*	0.00415

Table 6 (*Continued*)

							Maternal liver 20 min after dosing			171		
							Maternal liver 6 h after treatment			8.55		
							Maternal kidney 20 min after dosing			36.2		
							Maternal kidney 6 h after treatment			1.81		
							Fetuses 10 min after dosing			2		
							Fetuses 20 min after dosing			9.22		
							Fetuses 6 h after treatment			0.46		
Upmeier et al. [101]	2000	Rats (females, DA/Han)	10 mg/kg	Oral	GC–MS after BSTFA derivatization	12 ng/ml	Serum, 0.5 h after dosing			*26*	ng/ml	0.13
							Serum, 1.5 h after dosing			*31*	ng/ml	0.155
							Serum, 8 h after dosing			*22*	ng/ml	0.11
							Serum, 48 h after dosing			*1.75*	ng/ml	0.00875
			100 mg/kg				Serum, 0.33 h after dosing			*150*	ng/ml	0.075
							Serum, 2 h after dosing			*44*	ng/ml	0.022
							Serum, 8 h after dosing			*84*	ng/ml	0.042
							Serum, 48 h after dosing			*12.5*	ng/ml	0.00625
			10 mg/kg	i.v.			Serum, 0.33 h after dosing			*2100*	ng/ml	
							Serum, 2 h after dosing			*500*	ng/ml	
							Serum, 6 h after dosing			*450*	ng/ml	
							Serum, 48 h after dosing			*410*	ng/ml	
Yoo et al. [138]	2001	Rats (male)	10 mg/kg	Oral	HPLC w/ fluorescence detection	1 ng/ml	Serum 0.5 h			*8.9*	ng/ml	0.0445
							Serum 2 h			*5.75*	ng/ml	0.02875
							Serum 6 h			*2.4*	ng/ml	0.012
							Serum 24 h			*1.4*	ng/ml	0.007
			100 μg/kg	i.v.			Serum 10 min			*20*	ng/ml	
							Serum 0.5 h			*7.05*	ng/ml	
							Serum 2 h			*1.6*	ng/ml	
Kurebayashi et al. [96]	2002	Monkey (male)	100 μg/kg	Oral	HPLC w/ radioactivity, C-14-labeled BPA, S.A. 2.62 GBq/mmol (0.071 Ci/mmol)	3 ng/ml	Fecal collections for 168 h	2.14				
							Urine collections for 168 h	59.68				
							Plasma, 0.5 h after injection		0.098	≤1.5%	μg/ml	
							Plasma, 2 h after injection		0.028	≤1.5%	μg/ml	
		Monkey (female)					Fecal collections for 168 h	3.08				
							Urine collections for 168 h	37.21				
							Plasma, 0.5 h after injection		0.095	≤1.5%	μg/ml	
							Plasma, 2 h after injection		0.025	≤1.5%	μg/ml	
		Monkey (male)		i.v.			Fecal collections for 168 h	1.84				
							Urine collections for 168 h	63.2				
							Plasma, 0.5 h after injection		0.141		μg/ml	
							Plasma, 2 h after injection		0.032		μg/ml	
		Monkey (female)					Fecal collections for 168 h	1.95				

Table 6 (*Continued*)

							Urine collections for 168 h			50.37			
							Plasma, 0.5 h after injection				0.161		μg/ml
							Plasma, 2 h after injection				0.036		μg/ml
Uchida et al. [112]	2002	Monkey (pregnant, gestational day 150)	50 mg/kg	Subcut	GC–MS	?	Maternal serum 1 h after treatment				6.1		
							Fetal serum 1 h after treatment				1.7		
							Fetal liver 1 h after treatment				65		
							Fetal kidney 1 h after treatment				37.5		
Volkel et al. [104]	2002	Human	5 mg/person (around 77 μg/kg bw)	Oral	LC–MS/MS	1.37 ng/ml (6 nM)	Urine					No free BPA present	
						2.28 ng/ml (10 nM)	Blood					No free BPA present	
Domoradzki et al. [99]	2003	Rats (female)	10 mg/kg	Oral	HPLC w/ radioactivity, C-14-labeled BPA, S.A. 56 mCi/mmol (0.056 Ci/mmol), S.A. 200 mCi/mmol (0.20 Ci/mmol)	8-39 ng/g	Plasma, 15 min after dosing				0.716	ND	
							Plasma, 6 h after dosing				0.077	ND	
							Fecal collections for 96 h			77.82			
							Urine collections for 96 h			14.8			
		Rats (pregnant, gestational day 6)					Plasma, 15 min after dosing				0.37	ND	
							Plasma, 6 h after dosing				0.175	ND	
							Fecal collections for 96 h			64.86			
							Urine collections for 96 h			21.96			
							Embryos collected on GD 10			0			
		Rats (pregnant, gestational day 17)					Plasma, 15 min after dosing				1.028		
							Plasma, 6 h after dosing				0.194		
							Pooled plasma (to 12 h)					0.011–0.022	0.055–0.110
							Fecal collections for 96 h			72.03			
							Urine collections for 96 h			16.32			
							Embryos collected on GD 10			0.07			
		Rats (pregnant, gestational day 16)					Maternal plasma, 15 min after dosing				1.699	0.064	0.32
							Embryos collected 15 min after dosing				0.013	0.018	
							Yolk sac/placenta collected 15 min after dosing				0.342	0.095	
Kurebayashi et al. [97]	2003	Rats (males)	100 μg/kg	Oral	HPLC w/ BPA-derived radioactivity (verified by ESI/MS), C-14-labeled BPA, S.A. 2.62 GBq/mmol (0.071 Ci/mmol)	1 ng/g	Urine collections for 72 h	1.1	6.5	0.3			
							Fecal collections for 72 h	61	ND	ND			
							Bilary excretions within 18 h		41				
							Urine collections for 24 h			6.3			
							Urine collections for 48 h			10.1			
							Fecal collections for 48 h			81.6			
				i.v.			Urine collections for 24 h			8.4			

Table 6 (*Continued*)

							Urine collections for 48 h	12.5			
							Fecal collections for 48 h	77.6			
				Oral			Blood, 0.5 h		*0.018*	ND	
							Blood, 2 h		*0.0051*	ND	
							Blood, 24 h		*0.002*	ND	
				i.v.			Blood, 0.5 h		*0.0057*	ND	
							Blood, 2 h		*0.003*	ND	
							Blood, 24 h		*0.0022*	ND	
Zalko et al. [19]	2003	Mice (pregnant, gestational day 17)	25 μg/kg	Subcut	HPLC w/ radioactivity, tritium-labeled BPA, S.A. 572.2 kBq/μg (3.53 Ci/mmol), S.A. 811.3 kBq/μg (5.0 Ci/mmol)	?	Urine collections for 24 h	5.72			
							Fecal collections for 24 h	21.2			
							Maternal blood 24 h after treatment		2.2		ng/ml
							Maternal liver 24 h after treatment	2.48	11.95		ng/g
							Maternal ovaries 24 h after treatment		2.25		ng/g
							Maternal uterus 24 h after treatment		3.45		ng/g
							Amniotic fluid 24 h after treatment	0.34	4.85		ng/ml
							Fetuses 24 h after treatment	4.13	3.7		ng/g
		Mice (pregnant, gestational day 17)					Maternal plasma 0.5 h after treatment		2.36	1.06	ng/g
							Maternal plasma 2 h after treatment		0.78	0.15	ng/g
							Maternal plasma 24 h after treatment		0.17	na	ng/g
							Maternal liver 0.5 h after treatment		30.27	10.85	ng/g
							Maternal liver 2 h after treatment		9.47	1.51	ng/g
							Maternal liver 24 h after treatment		5.78	1.72	ng/g
							Placenta 0.5 h after treatment		21.94	15.98	ng/g
							Placenta 2 h after treatment		4.89	1.32	ng/g
							Placenta 24 h after treatment		1.00	0.06	ng/g
							Amniotic fluid 0.5 h after treatment		9.45	0.9	ng/g
							Amniotic fluid 2 h after treatment		5.31	0.1	ng/g
							Amniotic fluid 24 h after treatment		1.24	0.03	ng/g
							Fetuses 0.5 h after treatment		8.58	4.2	ng/g
							Fetuses 2 h after treatment		2.81	0.48	ng/g
							Fetuses 24 h after treatment		0.76	0.13	ng/g
		Mice (non-pregnant females)		Oral	HPLC w/ radioactivity		Maternal blood 24 h after treatment		0.027	ND	ng/g
							Maternal ovaries 24 h after treatment		0.021	ND	ng/g
							Maternal uterus 24 h after treatment		0.16	ND	ng/g

Table 6 (*Continued*)

							Maternal liver 24 h after treatment	0.0061	ND	ng/g
		Mice (pregnant, gestational day 17)	50 mg/kg	Subcut			Maternal liver 24 h after treatment	14,000	ND	ng/g
							Maternal ovaries 24 h after treatment	1,700	ND	ng/g
							matErnal uterus 24 h after treatment	9,400	ND	ng/g
							Amniotic fluid 24 h after treatment	6,400	ND	ng/g
							Fetuses 24 h after treatment	4,300	ND	ng/g
Domoradzki et al. [102]	2004	Rats (PND 4, 7 and 21, and adult 11 weeks)	1 mg/kg	Oral	HPLC w/ radioactivity, C-14-labeled BPA, S.A. 56 mCi/mmol (0.056 Ci/mmol), S.A. 200 mCi/mmol (0.20 Ci/mmol)	6–10 ng/g	Blood levels in PND4 rats 6 h after treatment	Female 0.37; male 0.38	Female 0.01; male 0.008	
							Blood levels in PND7 rats 6 h after treatment	Female 0.35; male 0.32		
							Blood levels in PND21 rats 6 h after treatment	Female 0.33; male 0.39		
			10 mg/kg			14–48 ng/g	Blood levels in PND4 rats 6 h after treatment	Female 3.55; male 5.56		
							Blood levels in PND7 rats 6 h after treatment	Female 3.57; male 3.37		
							Blood levels in PND21 rats 6 h after treatment	Female 3.52; male 3.18		
			1 mg/g			6–10 ng/g	PND 4 females, 0.25 h after dosing		*0.056*	
							PND 4 females, 1.5 h after dosing		*0.021*	
							PND 4 females, 18 h after dosing		*0.017*	
							PND 4 males, 0.25 h after dosing		*0.031*	
							PND 4 males, 1.5 h after dosing		*0.0064*	
							PND 4 males, 12 h after dosing		*0.026*	
							PND 7 females, 0.25 h after dosing		*0.21*	
							PND 7 females, 1.5 h after dosing		*0.023*	
							PND 7 females, 3 h after dosing		*0.021*	
							PND 7 males, 0.25 h after dosing		*0.043*	
							PND 7 males, 1.5 h after dosing		*0.012*	
							PND 7 males, 3 h after dosing		*0.03*	
							PND 21 females, 3 h after dosing		*0.0067*	
							PND 21 males, 0.25 h after dosing		*0.0076*	
							PND 21 males, 3 h after dosing		*0.0045*	
							11 weeks females		*NQ*	
							11 weeks males		*NQ*	
			10 mg/g			14–48 ng/g	PND 4 females, 0.25 h after dosing		*10.2*	
							PND 4 females, 0.75 h after dosing		*4.1*	
							PND 4 females, 1.5 h after dosing		*0.185*	

Table 6 (*Continued*)

							PND 4 females, 6 h after dosing	*0.097*		
							PND 4 males, 0.25 h after dosing	*49*		
							PND 4 males, 0.75 h after dosing	*1.1*		
							PND 4 males, 1.5 h after dosing	*2.2*		
							PND 4 males, 18 h after dosing	*0.091*		
							PND 7 females, 0.25 h after dosing	*5.9*		
							PND 7 females, 1.5 h after dosing	*0.44*		
							PND 7 females, 12 h after dosing	*0.094*		
							PND 7 males, 0.25 h after dosing	*1.15*		
							PND 7 males, 1.5 h after dosing	*0.2*		
							PND 7 males, 18 h after dosing	*0.053*		
							PND 21 females, 0.25 h after dosing	*0.1*		
							PND 21 females, 1.5 h after dosing	*0.2*		
							PND 21 females, 6 h after dosing	*0.11*		
							PND 21 males, 0.25 h after dosing	*0.057*		
							PND 21 males, 1.5 h after dosing	*0.15*		
							PND 21 males, 12 h after dosing	*0.026*		
							11 weeks females, 0.75 h after dosing	*0.063*		0.315
							11 weeks males, 0.25 h after dosing	*0.024*		0.12
							11 weeks males, 0.75 h after dosing	*0.012*		0.06
							11 weeks males, 1.5 h after dosing	*0.011*		0.055
Negishi et al. [139]	2004	Rats (female)	10 mg/kg	Oral	ELISA	12.5 ng/ml	Serum 0.5 h	*NQ*	μg/ml	
							Serum 2 h	0.011	μg/ml	0.055
							Serum 24 h	*NQ*	μg/ml	
		Chimpanzee 1 (female)					Serum 0.5 h	*0.32*	μg/ml	
							Serum 2 h	*0.14*	μg/ml	
							Serum 8 h	*0.051*	μg/ml	
		Chimpanzee 2 (female)					Serum 0.5 h	*0.093*	μg/ml	
							Serum 2 h	*0.079*	μg/ml	
							Serum 8 h	*0.045*	μg/ml	
		Cynomolgus monkeys (female)					Serum 0.5 h	*2.8*	μg/ml	
							Serum 2 h	*0.35*	μg/ml	
							Serum 6 h	*0.048*	μg/ml	
		Rats (female)	100 mg/kg				Serum 0.5 h	*0.58*	μg/ml	0.29
							Serum 2 h	*0.090*	μg/ml	0.045
							Serum 24 h	*0.020*	μg/ml	0.01
		Cynomolgus monkeys (female)					Serum 0.5 h	*5.4*	μg/ml	
							Serum 2 h	*4.1*	μg/ml	
							Serum 24 h	*0.12*	μg/ml	
		Rats (female)	10 mg/kg	Subcut			Serum 0.5 h	*0.49*	μg/ml	

Table 6 (*Continued*)

							Serum 2 h		*0.53*	µg/ml	
							Serum 6 h		*0.13*	µg/ml	
		Chimpanzee 1 (female)					Serum 0.5 h		*0.86*	µg/ml	
							Serum 2 h		*2.0*	µg/ml	
							Serum 24 h		*0.052*	µg/ml	
		Chimpanzee 2 (female)					Serum 0.5 h		*0.68*	µg/ml	
							Serum 2 h		*1.0*	µg/ml	
							Serum 24 h		*0.053*	µg/ml	
		Cynomolgus monkeys (female)					Serum 0.5 h		*0.64*	µg/ml	
							Serum 2 h		*5.9*	µg/ml	
							Serum 24 h		*0.034*	µg/ml	
		Rats (female)	100 mg/kg				Serum 0.5 h		*2.9*	µg/ml	
							Serum 2 h		*2.75*	µg/ml	
							Serum 24 h		*0.35*	µg/ml	
		Cynomolgus monkeys (female)					Serum 0.5 h		*6.0*	µg/ml	
							Serum 2 h		*16*	µg/ml	
							Serum 24 h		*2.9*	µg/ml	
Kurebayashi et al. [95]	2005	Rats (males)	500 µg/kg	Oral	Radioluminography of C-14-BPA-derived radioactivity, S.A. 2.62 GBq/mmol (0.071 Ci/mmol)	2 dpm/20 µl (<0.5 ng/ml)	Plasma 0.25 h	*34*	2.30% *≥0.78*	ng/ml	0.078
							Plasma 0.5 h	*28*		ng/ml	
							Plasma 2 h	*16*		ng/ml	
							Plasma 6 h	*17*	1.70% *≥0.29*	ng/ml	0.029
							Plasma 24 h	*9.2*	0.30%		
			100 µg/kg				Plasma 0.5 h	*7.1*		ng/ml	
							Plasma 2 h	*3.6*		ng/ml	
							Plasma 24 h	*2.7*		ng/ml	
			20 µg/kg				Plasma 0.5 h	*1.5*		ng/ml	
							Plasma 2 h	*1.4*		ng/ml	
							Plasma 24 h	*0.51*		ng/ml	
			500 µg/kg	i.v.			Plasma 0.5 h	*130*		ng/ml	
							Plasma 2 h	*55*		ng/ml	
							Plasma 24 h	*10*		ng/ml	
			100 µg/kg				Plasma 0.5 h	*29*		ng/ml	
							Plasma 2 h	*14*		ng/ml	
							Plasma 24 h	*4.2*		ng/ml	
		Rats (females)	500 µg/kg	Oral			Plasma 0.5 h	*14*		ng/ml	
							Plasma 2 h	*16.5*		ng/ml	
							Plasma 24 h	*7.2*		ng/ml	
			100 µg/kg				Plasma 0.5 h	*4.7*		ng/ml	
							Plasma 2 h	*3.6*		ng/ml	
							Plasma 24 h	*1.5*		ng/ml	
			20 µg/kg				Plasma 0.5 h	*0.51*		ng/ml	
							Plasma 2 h	*0.65*		ng/ml	
							Plasma 24 h	*0.23*		ng/ml	
			500 µg/kg	i.v.			Plasma 0.5 h	*160*		ng/ml	
							Plasma 2 h	*47*		ng/ml	
							Plasma 24 h	*14*		ng/ml	
			100 µg/kg				Plasma 0.5 h	*32*		ng/ml	
							Plasma 2 h	*8.9*		ng/ml	
							Plasma 24 h	*2.9*		ng/ml	
		Rats, 12 days gestation	500 µg/kg	Oral			Blood 0.5 h	43.32		ng/ml	
							Blood 24 h	4.33		ng/ml	
		Rats, 15 days gestation					Blood 0.5 h	37.51		ng/ml	
							Blood 24 h	3.83		ng/ml	
		Rats, 18 days gestation					Blood 0.5 h	30.99		ng/ml	
							Blood 24 h	10.79		ng/ml	
		Rats (lactating females, 11 days after giving birth)					Plasma 0.5 h	*27*		ng/ml	
							Plasma 2 h	*22*		ng/ml	
							Plasma 24 h	*14*		ng/ml	
							Plasma 48 h	*7.7*		ng/ml	

Table 6 (*Continued*)

							Milk 0.5 h			*1.1*		ng/ml	
							Milk 2 h			*1.2*		ng/ml	
							Milk 24 h			*3.9*		ng/ml	
							Milk 48 h			*1.9*		ng/ml	
Volkel et al. [105]	2005	Human	25 μg/person (around 0.38 μg/kg)	Oral	LC–MS/MS	1.14 ng/ml	Urine levels in females within 5 h of treatment	ND – 2	75				
							Urine levels in males within 5 h of treatment	ND – 2	85				
							Plasma levels within 5 h of treatment	ND	Detected				
Moors et al. [140]	2006	Rats (pregnant, gestational day 18)	10 mg/kg	i.v.	GC–MS after derivatization	15 ng/ml	Maternal plasma, 5 min			3.8	2.9	μg/ml	
							Maternal plasma, 2 h			0.7	0.3	μg/ml	
							Maternal plasma, 6 h			0.8	0.1	μg/ml	
							Maternal liver, 0.5 h			9.3			
							Maternal liver, 2 h			*4.1*			
							Maternal liver, 6 h			*4.7*			
							Maternal kidney 0.5 h			8.6			
							Maternal kidney 2 h			*0.65*			
							Maternal kidney 6 h			*0.86*			
							Maternal uterus 0.5 h			6.2			
							Maternal uterus 2 h			*0.91*			
							Maternal uterus 6 h			*1.3*			
							Maternal placenta 0.5 h			4.0			
							Maternal placenta 2 h			*0.65*			
							Maternal placenta 6 h			*0.99*			
			10 mg/kg to the mother	i.v.			Fetal liver, 0.5 h			3.3			
							feTal liver, 2 h			*0.84*			
							Fetal liver, 6 h			*1.2*			
							Fetal homgenate 0.5 h			2.4			
							Fetal homogenate 2 h			*0.44*			
							Fetal homogenate 6 h			*0.92*			
Savabieasfahani et al. [141]	2006	Sheep (pregnant Suffolk ewes), gestational day 50	5 mg/kg daily	Subcut, 20 days	HPLC, fluorescence detection	10 ng/ml	Maternal plasma, after 20 days of daily BPA treatment				*45*	ng/ml	
		Gestational day 70		Subcut, 40 days			Maternal plasma, after 40 days of daily BPA treatment				*55*	ng/ml	
		Gestational day 90		Subcut, 60 days			Maternal plasma, after 60 days of daily BPA treatment				37.4	ng/ml	
Takeuchi et al. [27]	2006	Rats (female)	50 mg/kg	Subcut	ELISA	0.5 ng/ml	Intact, serum 1h			*0.66*		μg/ml	
							Intact, serum 2 h			0.7496		μg/ml	
							Intact, serum 3 h			*0.64*		μg/ml	
							Intact, serum, 2 h			*0.65*		μg/ml	
							Ovx, serum, 2 h			*0.68*		μg/ml	
							Ovx+TP 0.01, serum, 2 h			*0.79*		μg/ml	
							Ovx+TP 0.1, serum, 2 h			*0.98*		μg/ml	
							Ovx+TP 1.0, serum, 2 h			*1.4*		μg/ml	
			0 mg/kg (basal)				Intact, serum, 0 h (basal)			0.00438		μg/ml	
							Ovx, serum, 0 h (basal)			0.0041		μg/ml	
							Ovx+TP 0.01, serum, 0 h (basal)			0.00451		μg/ml	
							Ovx+TP 0.1, serum, 0 h (basal)			0.00534		μg/ml	
							Ovx+TP 1.0, serum, 0 h (basal)			0.00576		μg/ml	
Tominaga et al. [103]	2006	Rats (female)	10 mg/kg	Oral	LC–MS/MS w/ ESI	0.2 ng/ml	Serum 0.5 h				*2.1*	μg/l =	0.0105
							Serum 2 h				*0.63*	ng/ml	0.00315
							Serum 24 h				*0.62*	ng/ml	0.0031
		Chimpanzees (female)					Serum 0.5 h				*5.3*	ng/ml	
							Serum 2 h				*2.9*	ng/ml	

Table 6 (*Continued*)

							Serum 24 h		*0.35*	ng/ml	
		Cynomolgus monkeys (female)					Serum 0.5 h		*9.5*	ng/ml	
							Serum 2 h		*6.6*	ng/ml	
							Serum 24 h		*0.4*	ng/ml	
		Rats (female)	100 mg/kg				Serum 0.5 h		*48*	ng/ml	0.024
							Serum 2 h		*5.9*	ng/ml	0.00295
							Serum 24 h		*4.2*	ng/ml	0.0021
		Cynomolgus monkeys (female)					Serum 0.5 h		*17.5*	ng/ml	
							Serum 2 h		*24*	ng/ml	
							Serum 24 h		*1.4*	ng/ml	
		Rats (female)	10 mg/kg	Subcut			Serum 0.5 h		*740*	ng/ml	
							Serum 2 h		*370*	ng/ml	
							Serum 24 h		*0.84*	ng/ml	
		Chimpanzees (female)					Serum 0.5 h		*510*	ng/ml	
							Serum 2 h		*580*	ng/ml	
							Serum 24 h		*16.7*	ng/ml	
		Cynomolgus monkeys (female)					Serum 0.5 h		*640*	ng/ml	
							Serum 2 h		*4100*	ng/ml	
							Serum 24 h		*34*	ng/ml	
		Rats (female)	100 mg/kg				Serum 0.5 h		*2300*	ng/ml	
							Serum 2 h		*2250*	ng/ml	
							Serum 24 h		*9*	ng/ml	
		Cynomolgus monkeys (female)					Serum 0.5 h		*3400*	ng/ml	
							Serum 2 h		*6950*	ng/ml	
							Serum 24 h		*1500*	ng/ml	
		Rats (female)	10 mg/kg		LC–MS/MS w/ ESI, after enzymatic deconjugation		Serum 0.5 h	*134*		ng/ml	
							Serum 2 h	*98.5*		ng/ml	
							Serum 24 h	*17.3*		ng/ml	
		Chimpanzees (female)					Serum 0.5 h	*975*		ng/ml	
							Serum 2 h	*440*		ng/ml	
							Serum 24 h	*8.8*		ng/ml	
		Cynomolgus monkeys (female)					Serum 0.5 h	*8800*		ng/ml	
							Serum 2 h	*2000*		ng/ml	
							Serum 24 h	*33*		ng/ml	
Xiao et al. [142]	2006	Rats (male)	100 mg/kg	Oral	HPLC w/ fluorescence detection	2.8 ng/ml	Serum 1 h		*1.4*	μg/ml	0.7
							Serum 2 h		*2.8*	μg/ml	1.4
							Serum 24 h		*1.8*	μg/ml	0.9
							Serum 48 h		*0.88*	μg/ml	0.44
							Serum 72 h		*0.35*	μg/ml	0.175
				Oral w/NP			Serum 1 h		*2.3*	μg/ml	1.15
							Serum 2 h		*3.3*	μg/ml	1.65
							Serum 24 h		*2.9*	μg/ml	1.45
							Serum 48 h		*0.77*	μg/ml	0.385
							Serum 72 h		*0.29*	μg/ml	0.145

Numbers in italics have been digitized from the published figures and are approximate. Scaling by approximation of linearity of circulating level of BPA with dose within dosing method. Current reference dose for BPA is 50 μg/kg bw/day. Subcut, subcutaneous; i.p., intraperitoneal; i.v., intravenous; NQ, not quantifiable; ND, not detected; PND, postnatal day; NP, nonylphenol.

sure at higher doses. This allows for estimates of the circulating levels of parent, unconjugated BPA in animals that are showing adverse effects in low-dose *in vivo* studies, which has not been measured directly in any study of oral pharmacokinetics. The estimate of the ranges of circulating levels of BPA that are active in low-dose animal studies will be compared to current measurements of circulating levels of parent, unconjugated BPA that have been measured in human blood and tissues (Table 1), and to the concentrations of BPA that are active in human and animal cell culture studies *in vitro* (reviewed in [3]).

5.2. Direct rodent studies of metabolism of BPA administered orally in the low-dose range

A substantial proportion of the literature on low-dose effects has used oral exposure. Unfortunately, very few studies have measured BPA in the blood of animals treated with low doses of BPA (<5 mg/kg bw), and none have measured following serial oral doses.

In the published study most relevant to low-dose developmental effects observed in rodents, tritiated BPA of high specific activity was orally administered to gestational day 17 pregnant mice at 25 μg/kg [19]. While unconjugated BPA was not measured after oral dosing in this study, the total radioactivity present in blood was measured at 0.027 ng BPA equivalents/g at 24 h after oral dosing, the only time point measured in the study [19]. Since unconjugated BPA is only a fraction of the total metabolites circulating after administration, the circulating level of unconjugated BPA in the study would be below the measured value of total BPA-derived radioactivity. In a second published study of oral low-dose pharmacokinetics [95], male rats were dosed orally with 500 μg BPA/kg body weight and free (unconjugated) BPA was calculated in blood at approximately 0.8, 0.3 and 0.03 ng/ml at 15 min, 6 and 24 h after dosing, respectively (Table 6). Only total radioactivity (comprised mostly of conjugated BPA) in blood after oral dosing was reported in the same study at lower doses of BPA [95] or in other studies at low oral doses [96,97,19] including in pregnant animals. The median human level of unconjugated BPA (∼2 ng/ml) was above the levels of unconjugated BPA in low-dose exposed rodents.

BPA is thought to bind to plasma proteins in rodents, monkeys and humans (reviewed in [91]). Because pharmacokinetics are altered by protein binding, the potential uptake of BPA into other tissues, including estrogen-target tissues, may be affected. This is a topic that requires additional study to properly address its implications for risk assessment purposes [98].

5.3. Processes used to estimate the range of circulating BPA in rodents in response to different doses of BPA, and comparison to median human exposure levels

While not available directly in any one study, existing published data can be used to estimate the circulating level of BPA in animals responding to low doses of BPA, and these estimated levels can be compared to current human circulating levels. This can be derived by addressing the following issues linking the oral low-dose exposure studies in animals, reports of the BPA pharmacokinetics in animals at different doses, and the reported human circulating levels of BPA. This process involves the following published conclusions: the importance of route of exposure (oral route selected), the form of BPA in circulating in blood (unconjugated, biologically active BPA), the reported proportionality of circulating level with dose across a wide range of doses, similar pharmacokinetics in non-pregnant and pregnant adults [99], only slight increases in circulating BPA following one exposure compared to multiple exposures [100], and rodent pharmacokinetics compared to pharmacokinetics in humans. These published conclusions link over 40 animal studies of adverse effects at oral doses below the reference dose for BPA, 11 studies of BPA pharmacokinetics following oral dosing, 9 reports of circulating BPA levels in pregnant and non-pregnant women, and 19 reports of effects BPA at or below 10 nM (2.3 ng/ml) on human and animal cell function in mechanistic studies *in vitro* [3].

As indicated above, the USEPA reference dose for BPA is currently 50 μg/kg/day. There are over 40 studies reporting effects at or below this RfD [4]. However, data are very limited regarding blood or tissue levels at or below the reference dose. To estimate these circulating levels for comparison to current human exposure (Table 1), the following steps were used to estimate the range of blood levels that would occur if a 50 μg/kg dose were administered to rodents: of the 21 acute metabolic studies (Table 6) in which BPA was administered to rodents, 17 contained data on blood levels of BPA and metabolites after oral administration, and of these 17 studies, 11 contained measurements of unconjugated BPA, which is the form measured in blood in human studies. Also, as indicated previously, only unconjugated BPA is biologically active. We thus used data from these 11 studies in this analysis to describe the pharmacokinetics of BPA after oral administration to adult rodents (pregnant females, non-pregnant adult females and adult males).

There are several bases for the following analysis. Because all but one of the metabolism studies were performed at doses higher than 50 μg/kg, this raised the question of whether it is valid to use the high dose studies to estimate blood levels that would occur after administration of the RfD. For this analysis to be valid, it was necessary to determine whether there was proportionality of circulating level with administered dose. This is in fact supported by the conclusions of several studies [90,101,102,95,103] using an oral route of exposure, which is why only data from this route of exposure was used in this analysis.

We then used the data from all 11 studies at a number of different doses, and linearly scaled the reported results to a single administered dose of 50 μg/kg. For example, circulating levels reported after dosing at 500 μg/kg were divided by 10, while circulating levels after dosing at 10 mg/kg were divided by 200, in order to scale the reported data to 50 μg/kg. The results of this scaling are shown in the last column of Table 6. The complete set of 18 data sets from all 11 studies are graphed in Fig. 1. The data are presented as a log–log plot, which allows data spanning a wide range to be displayed on a single graph. In addition, the time-courses were approximately linear in the log–log plot. Even though there were differences in the values reported in

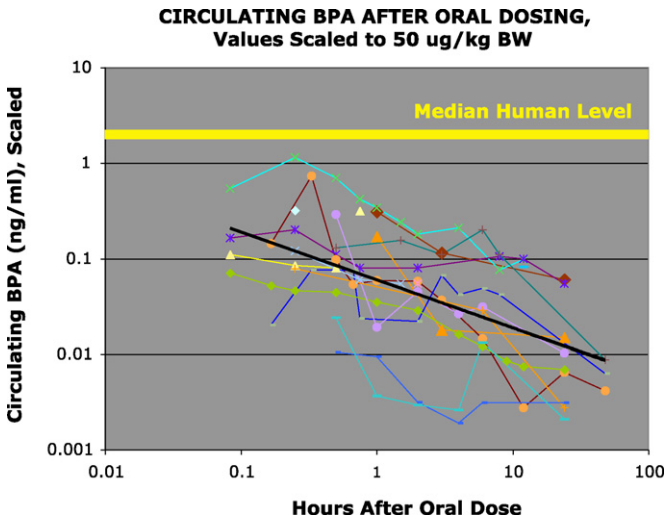

Fig. 1. Scaled values of circulating BPA after oral dosing. The complete set of 17 data sets of circulating BPA at times after oral dosing of adults from 11 studies of Table 6, last column, where unconjugated BPA was measured or could be calculated, are graphed in the figure. All data recovered from publications and figures are plotted, not just the selected time points listed in Table 6. The data are presented as a log–log plot, which allows data spanning a wide range to be displayed on a single graph. In addition the time-courses were approximately linear in the log–log plot. The black line shows the power regression curve (linear regression of log BPA vs. log time) of all of the individual BPA measures against time after oral dose.

these 11 studies with regard to measured unconjugated BPA in blood, in no case did any data point from these 11 studies reach the median human level of unconjugated BPA.

Subsets of the data shown in Fig. 1 are presented in Fig. 2 to address two issues. One is the validity of scaling circulating levels from different doses to one reference dose, specifically, the impact of the administered dose on the data obtained after the scaling procedure (Fig. 2 A–C); publications report proportionality with dose where encountered [90,95,101–103]. The second is variability due to the type of animal (pregnant female, non-pregnant adult female or adult male) used in the study (Fig. 2 E–G) to address pooling the small set of pregnant animal data with the larger set of non-pregnant animal data; the conclusion of at least one report is that the pharmacokinetics do not vary between non-pregnant and pregnant rodents [102].

Fig. 2 Panel A shows the results from scaling data to 50 μg/kg across the extremes of the complete data set for administered dose: from 1 g/kg, 0.5 mg/kg and 25 μg/kg (represented as a single point), and the scaled profiles were quite similar, with all points close to the linear regression line (dark black line in the figure) of all data from all studies. Further, in Panel B, a plot of all the data for 100 mg/kg administered dose, and Panel C, the data for 10 mg/kg administered dose, there was again no trend that contradicted the assumption of proportionality based on this analysis. Taken together, the data in Panels A–C support proportionality of circulating unconjugated BPA based on administration of high doses down to the RfD.

The second issue of animal type was important because many of the *in vivo* animal studies involve administration of BPA to pregnant female rodents, and there are a number of biomonitoring studies that have addressed the blood levels of unconjugated BPA in pregnant and non-pregnant women. However, there are only a limited number of metabolism studies that involved pregnant rodents. The data in Panel D from studies with pregnant rodents were within the range of the data from non-pregnant females (Panel E) and adult males (Panel F). Thus, the scaling procedure did not appear to show a bias based on the type of animal used in the study. As indicated previously, this finding is consistent with the conclusion of Domoradzki et al. [102] that BPA metabolism does not differ significantly between pregnant and non-pregnant females.

The data in Figs. 1 and 2 support scaling and combining metabolism data across a wide range of doses and species to estimate circulating levels of BPA in rodents when administered doses within the "low dose" range that cause adverse effects. Specifically, from the combined data in Fig. 1, at 1 h after oral BPA administration, the blood levels of unconjugated BPA ranged from 0.003 to 0.3 ng/ml. At 24 h, the values ranged from 0.002 to 0.06 ng/ml (Table 6). Peak levels of BPA achieved in the first 30 min after oral administration ranged from 0.01 to 1.14 ng/ml. Median values across the studies were 0.11 ng/ml at 0–30 min, 0.047 ng/ml at 1 h, and 0.007 ng/ml at 24 h.

There are two main conclusions from these findings. The first is that many adverse effects that have been reported in animals at or below the RfD [4] occur in animals at circulating levels of unconjugated BPA below median current human exposure levels (~1–3 ng/ml). Second, unless humans metabolize BPA much more slowly than animals, human exposure to BPA would have to exceed the reference dose of 50 μg/kg/day. In fact, it has been reported that the metabolism and clearance of BPA is more rapid in humans than in rodents [91], suggesting that human exposure to BPA is substantially higher than the RfD based on a comparison to blood levels achieved in rodents at all time points after BPA exposure scaled to the reference dose of 50 μg/kg/day. Given an assumption of equivalent pharmacokinetics in humans and rodents, at 1 h after administration of 50 μg/kg, rodent blood levels are over 10-fold below median human blood levels, and to achieve these levels humans would have to be exposed to a dose greater than 500 μg/kg. If human metabolism and clearance are more rapid than rodent clearance, which is concluded by studies that have addressed the issue [104,105,91], then the human exposure to achieve the current human circulating levels would have to be well above 500 μg/kg/day (greater than 32 mg/day/adult considering a 65 kg human). This is consistent with the observation of Shin at al. [100]; in their pharmacokinetic models, an oral intake of 100 mg BPA/day would explain the mean human circulating level of 1.49 ng/ml reported by Takeuchi and Tsutsumi [25]. Therefore, these models indicate that (i) humans are exposed to BPA at a much higher level than has been estimated from known exposure sources, and/or (ii) humans are exposed through multiple routes, making the metabolic response different from that observed in animal models, and/or (iii) metabolism of BPA following chronic, low-dose exposure is not predicted by the acute high-dose studies used to generate the current pharmacokinetic models. Finally, while many responses have been observed in human and animal cells at and below concentrations of 1 nM (0.23 ng/ml) [3] median

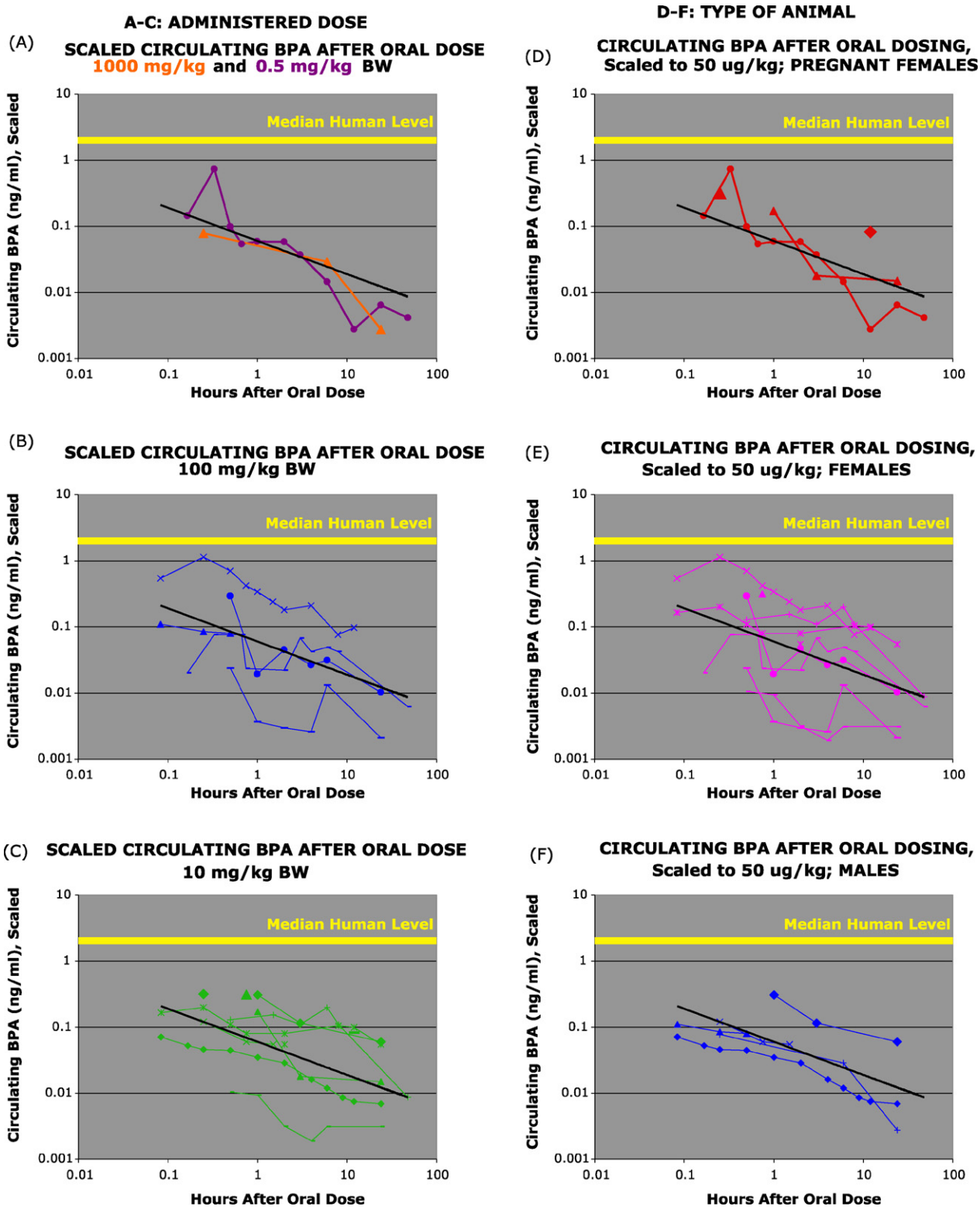

Fig. 2. Subsets of the data of Fig. 1 grouped by dose (A–C) or by animal type (D–F). Subsets of the data from Fig. 1 are presented to address (1) the validity of scaling circulating levels from different doses to one reference dose, and (2) variability due to the type of animal (pregnant female, non-pregnant adult female or adult male). The black line shows the power regression curve (linear regression of log BPA vs. log time) of all of the individual BPA measures against time after oral dose, for reference to the individual data subsets. Panel A graphs the circulating levels scaled from the extremes of oral doses, 1 g/kg bw (orange) and 500 μg/kg bw (purple). Panel B graphs all circulating levels after oral dose of 100 mg/kg, and Panel C graphs levels reported after 10 mg/kg. Within the variation between publications, there was no apparent trend of scaled level with dose. Panel D graphs the scaled circulating levels in reports of oral dosing in pregnant females from four data sets, two consisting of single time points. Panel E graphs circulating levels after oral dosing of adult, non-pregnant females, and Panel F graphs levels reported after dosing adult males. Within the variation between publications, there was no apparent trend of scaled level with animal type, although differences between adult females and adult males were reported within individual publications that compared both within the same study (see text).

human blood levels of unconjugated BPA are clearly higher. It is thus completely plausible that at current human exposure levels, BPA is impacting cell and organ function in humans (see [3] and [4] for review).

5.4. Comparisons of human exposure levels and animal studies

The few studies that have examined BPA levels in animals following low level exposure have found blood concentrations in the sub ng/ml range [19,95]. These levels are thus lower than concentrations that have been measured in human blood (Table 1). Collectively, these data indicate that the levels being studied in animals which lead to biological effects are relevant to current human exposure levels; current human exposures are higher than the levels in animals responding to BPA. Because few comprehensive studies have focused on human metabolism of BPA, and differences in pharmacokinetics are suspected between species, additional research in this area is needed.

One additional area of research that has remained largely unexplored is the potential difference in BPA metabolism between different groups of people. Several animal studies have indicated strain differences in rats and mice with regard to BPA metabolism. While some human studies have examined polymorphisms for enzymes involved in BPA metabolism [106,45], studies using larger and more widespread populations are needed.

5.5. Animal models of BPA metabolism: digestion and excretion

Because BPA is suspected to enter the human body mainly through the oral route, several studies have examined the absorption and metabolism of BPA in the intestine and liver. One comprehensive study compares the metabolism and excretion of BPA in rats dosed with 0.10 mg radiolabeled BPA/kg body weight either by oral or intravenous (i.v.) exposure [97]. This relatively low dose was chosen because previous studies used oral doses of 100 mg/kg or more, levels thought to saturate the metabolic and excretory mechanisms responsible for the elimination of BPA from the body. With this lower dose, the i.v. and oral dosing led to a urinary excretion of 8.4 and 6.3% of the radioactivity, respectively, within 24 h of treatment. Fecal excretion from the i.v. and oral dosing was 77.6 and 81.6% of the administered dose, respectively. Collectively, Kurebayashi et al. [97] concluded that there are similar metabolic kinetics in these two modes of exposure, and that fecal excretion is the main route of BPA elimination in the rat.

Several studies have determined that the liver plays an essential role in metabolizing BPA *in vivo* in animal models. Glucuronidation is a metabolic pathway in the liver used to excrete both endogenous and exogenous compounds; BPA–glucuronide has been shown by many to be the major BPA metabolite in animals and humans and has little or no estrogenic activity in several *in vitro* assays. Yokota et al. [107] identified and examined UGT2B1, a liver enzyme responsible for glucuronidation of BPA and other xenoestrogens. Interestingly, a study of rat liver S9 fractions, containing both microsomal and cytosolic fractions, indicates that the liver may also produce a BPA metabolite with increased estrogenic activity [108]. However, the authors of this study acknowledge that this metabolic pathway is probably not significant under normal circumstances, and is likely only active when glucuronidation is efficient.

An additional study used segmented everted rat intestine to measure transport and conjugation of BPA in each portion of the intestine [109]. Addition of BPA to the mucosal side of the intestine led to absorption and transport to the serosal side; there were no significant differences in this transport among the five portions of the intestine. However, the appearance of BPA on the serosal side was accelerated by treatment with a high dose (100 μM). This study also examined glucuronidation of BPA by each segment of the rat intestine. Following BPA administration, BPA–glucuronide was expelled into the mucosal side and transported to the serosal side of the intestine; the level increased with the incubation time. Interestingly, in the small intestine, the greatest amount of BPA–glucuronide was secreted into the mucosal side, but in the colon, secretion was greatest to the serosal side. The authors therefore suggested that while the proximal intestine may protect against the absorption of BPA in rats, the colon may be more susceptible to BPA transport. The authors also proposed the possibility that BPA–glucuronide secreted into the mucosal side of the proximal intestine could be deconjugated by glucuronidases produced by bacteria in the colon. This BPA would then be free and could be reabsorbed [110,109]. These authors also suggest that the effects of BPA may be enhanced by repeated, continuous exposure [110].

5.6. Animal models of BPA metabolism: transfer to the developing fetus

The metabolic changes associated with pregnancy could cause alterations in the metabolism and excretion of BPA from both pregnant animals and women. Takahashi and Oishi [111] examined oral administration of 1 g BPA/kg to pregnant rats on day 18 of gestation. BPA was detected in maternal blood within 10 min of dosing (2.89 μg/g), reached a peak concentration at 20 min after dosing (14.7 μg/g) and gradually decreased over a period of 10 h. BPA was also detected in fetuses within 10 min of dosing (2.00 μg/g); a maximum concentration was reached at 20 min (9.22 μg/g) and levels gradually decreased with time. The concentration after 6 h was 5% of the level detected at maximum. This study illustrated that absorption of BPA by both the pregnant mother and the fetus in this model was rapid and the placenta did not block BPA transmission. An additional study of mice and Japanese monkeys dosed with 100 mg/kg BPA during pregnancy showed that BPA could be detected in several fetal tissues, including serum, liver, brain, uterus and testes within 30 min (mice) and 1 h (monkeys) of treatment [112].

Zalko et al. [19] demonstrated in a mouse model that much lower doses (25 μg/kg) of BPA were also able to cross the placental barrier. Twenty-four hours after BPA administration, fetuses accounted for 4% of the administered radioactivity, with an average of 3.7 ng/g. The placenta maintained 0.55% of the

administered BPA (3.14 ng/g) and the amniotic fluid contained 0.34% (4.85 ng/ml).

5.7. Human metabolism of BPA: acute exposure studies

Only a small number of studies have attempted to determine the pharmacokinetics of BPA metabolism in human subjects (Table 6). Volkel et al. [104] administered 5 mg radioactive BPA/person (54–90 μg/kg body weight) and reported that elimination of BPA was complete within 24 h of dosing. Maximal plasma concentrations were reached 80 min after dosing and rapidly declined for the next 6 h. BPA was detected only in its glucuronidated form, and not as free BPA. The results of this study indicated that in the human, BPA was absorbed from the gastrointestinal tract quickly, conjugated with glucuronic acid in the liver, and BPA–glucuronide was rapidly filtered from the blood by the kidneys and excreted in urine. This metabolic pathway differed from that of the rat, where a large amount of BPA–glucuronide is transported into bile and enters the digestive system [107].

In another metabolic study, BPA was administered (25 μg/person) and then free BPA and BPA conjugates were measured in urine and blood by isotope dilution LC–MS; LODs were 1.14 ng/ml (BPA) and 10.1 ng/ml (BPA–glucuronide) [105]. In the three men examined, 85% of the applied BPA dose was recovered in urine after 5 h, mostly as BPA–glucuronide. In the three women examined, 75% of BPA was recovered as BPA–glucuronide after the same period of time, indicating the potential for some gender differences in BPA absorption, metabolism and/or excretion, as suggested by other studies [33,35]. In two of six individuals, free BPA was detected in the urine at levels of approximately 1 ng/ml; free BPA was not detected in the urine of the other four individuals [105], although this study was limited by its small numbers of subjects and relatively poor sensitivity. The levels of BPA in blood samples following this acute exposure were not reported in this study.

Some authors have suggested that human microsomes may not be able to glucuronidate BPA as extensively as rat microsomes, making the metabolic kinetics different for the human compared to other mammals [113]. Alternatively, Pritchett et al. [114] predict that when metabolic levels measured in isolated hepatocytes are extrapolated to the entire liver, the hepatic capacity for BPA glucuronidation is higher in humans than in mice or rats. Additional studies are needed to rectify these theories. In the study of Yoshihara et al. [108] discussed above, rat liver extracts were found to produce a BPA metabolite with increased estrogenic activity. Interestingly, this metabolite was also produced *in vitro* by mouse, monkey and human liver S9 fractions, suggesting that some aspects of BPA metabolism may be conserved across mammalian species.

Together, data from these studies and others are being used to generate models for BPA kinetics following intravenous and oral route exposures [91]. These models indicate that BPA metabolism may be different in rats and humans, including endpoints such as BPA clearance rates, intestinal glucuronidation, and excretion rates. Additional studies are needed to validate these models or produce new ones. However, as already noted, these models are based on acute, single exposure kinetics instead of the chronic exposures that are most relevant to humans exposed environmentally.

6. Summary

Dozens of studies have been dedicated to monitoring levels of BPA in human tissues, blood, urine, and other fluids; extensive evidence exists to demonstrate that most humans are exposed to BPA. Unconjugated BPA has been measured repeatedly in human blood (serum and plasma), breast milk, amniotic fluid, and placental tissue in the low ng/ml or ng/g range using various analytical techniques. Additionally, BPA conjugates have been repeatedly found in the low ng/ml range in the urine of over 90% of individuals tested in several countries and continents. Of particular concern are the levels that have been detected in the blood of pregnant women, fetal blood, umbilical cords, placenta and amniotic fluid. Because the developing fetus is acutely sensitive to hormones and chemical exposures, the levels detected are a cause for concern.

It has been proposed that xenoestrogens such as BPA could play a role in reproductive cancers (testicular, prostate, breast, uterine, ovarian, etc.), fertility problems (low sperm count, decreased sperm quality), and other endocrine related endpoints. At this time, only a few small studies have explored the associations between BPA levels and human health issues. However, these limited data indicate that additional studies are warranted on human health and BPA exposure. Currently, there is limited evidence to suggest that BPA levels vary between men and women and/or with several endocrine-related syndromes and diseases, including polycystic ovarian syndrome and obesity, which are brought about in animals by exposure to low doses of BPA.

There is extensive evidence that many consumer products contain and release BPA. BPA content has been measured in food containers, epoxy resins, plastics, baby bottles, and dental sealants, and leaching rates have been measured from many of these products under normal conditions of use. BPA has been detected in a wide range of foods stored in cans with epoxy resins. Additionally, BPA has been measured in freshwater, seawater, landfill leachates, air, and dust particles. Collectively, these studies indicate that exposure to BPA is widespread, from many different sources in the environment. There are several studies that have generated estimates of current exposure from leaching levels of consumer products. These studies have estimated that human exposure ranges from under 1 μg/kg/day to almost 5 μg/kg/day (0.325 mg/day/adult). However, pharmacokinetic modeling data suggest that oral intakes up to 100 mg/day/adult would be required to explain the reported human circulating levels. Additional studies and mathematical models of potential exposures are needed, particularly because many sources of BPA exposure have been identified.

The consistent finding that BPA is detected in almost all individuals in developed nations implies that humans are exposed to BPA continuously. Because of the rapid metabolic clearance of BPA, and the measurable levels of BPA that have been detected in human blood and urine, Welshons et al. [8] have identified two potential issues: (1) BPA intake may be actually much higher

than has been suggested, and/or (2) long-term, daily intake leads to bioaccumulation of BPA, leading to steady-state levels that are not represented by any of the current models for BPA metabolism based on single, acute administration.

The levels of BPA measured in human serum, urine and other tissues are within the range shown to cause effects in laboratory animals, and impact cell function in mechanistic studies in cell culture. Therefore, it is plausible and even likely that these levels are biologically active in humans, with obvious potential to cause disease or dysfunction. This review has highlighted several areas of research that must be addressed to answer additional questions that have been posed.

7. Conclusions and levels of confidence for different outcomes

7.1. Based on available evidence, we are confident of the following

7.1.1. BPA levels in human tissues and fluid

Human studies have shown that most children, as well as adult men and women, including pregnant women, have measurable levels of BPA in body fluids and tissues sampled. Unconjugated BPA has been measured repeatedly in human blood (serum and plasma) with a central measure of the distribution in the 0.3–4.4 ng/ml range (1–19.4 nM), and in breast milk, amniotic fluid, and placental tissue in the low ng/ml or ng/g range. The measurements of BPA in maternal serum, fetal serum, umbilical cord blood, amniotic fluid and placenta indicate that the developing human fetus may be exposed to BPA in the 1–3 ng/ml range (4–13 nM). The ng/ml levels in human serum are similarly measured by several analytical techniques and ELISA, if the method sensitivity is at or below 0.5 ng/ml. Studies using mass spectrometry detection methods are considered highly reliable, while there is considerably less confidence in studies employing ELISA.

Conjugates of BPA in urine are measured in the low ng/ml range, and are repeatedly found in over 90% of individuals tested (8 of 13 cited publications), including a study of a reference adult population.

7.1.2. Sources of BPA in the environment

There is extensive evidence that many consumer products contain and release BPA. There is also extensive evidence that many of these products leach BPA under normal conditions of use. BPA has been detected in baby bottles, epoxy resins, and other consumer plastics. BPA has also been detected in a wide range of foods stored in cans with epoxy resins. There is very good evidence to indicate that BPA can be detected in environmental samples, including air, dust and water. Evidence for this is supported by studies of landfill leachates which indicate substantial release of BPA from landfills.

7.1.3. BPA metabolism in humans and animals

There is extensive evidence for the kinetics of BPA metabolism in rodent models following acute exposures to relatively high doses. Acute studies in both animals and humans indicate rapid metabolism and clearance. BPA can be detected in the blood shortly after treatment, and in collected urine and feces. However, acute studies do not reflect the situation in humans, where exposure is more likely chronic and low-level. Therefore, additional studies of chronic, low-level exposure to BPA are needed in both animal models and human subjects.

7.2. Based on the available evidence, we consider the following to be likely but requiring confirmation

7.2.1. Levels of BPA in the environment

Many studies have examined leaching levels from dental sealants immediately after and several hours after application. However, different results have been obtained, likely based on variability within each product, differences in analytical methods, and sensitivities of detection. The results of these experiments indicate it is likely that sufficient BPA leaches from some but not all dental sealants immediately after application to elevate baseline urine BPA. Several studies, although small, suggest that BPA released from (some) dental sealants does not account for or may not significantly impact baseline BPA levels in saliva and urine. However, additional randomized controlled clinical studies with sufficient numbers of subjects and high resolution techniques are needed to examine leaching rates after several hours, days, and longer. Data regarding chronic exposures from dental sealants are currently lacking.

There are several studies that have generated estimates of current exposure from leaching levels of consumer products. These studies have estimated that human exposure ranges from less than 1 μg/kg/day to almost 5 μg/kg/day. More studies and mathematical models of potential exposures are needed, particularly because many environmental sources of BPA exposure have been identified.

7.2.2. BPA metabolism in humans and animals

There is some evidence that BPA metabolism in rodents differs from metabolic endpoints in primate models. In rodents, the majority of BPA is excreted in the feces, but in the monkey, BPA is excreted via urine. Additional experiments in primates and humans would help clarify these apparent pathways, and allow for further discussion of their implications. Completing these studies with chronic, low-doses is also necessary.

7.3. Research to be pursued in future scientific investigations

7.3.1. BPA levels in human tissues and fluids

At this time, only a single study has examined BPA levels in follicular fluid. The levels found in these samples have important implications for fertility and human development because of findings of aneuploidy in mice and actions in *in vitro* models. Well-controlled epidemiological studies in women are necessary to assess potential impact on IVF procedures.

Studies are needed to examine BPA levels in human tissues. At this time, studies have examined BPA levels in placental tissue and amniotic fluid. Additional studies are needed to measure BPA in fat and other organ tissues. These data are needed to

examine the relationship between serum BPA levels and tissue levels. Additionally, these data will provide the basis for studies of bioaccumulation.

Finally, studies that have examined and measured ng/ml BPA levels in human tissues and fluids have thus far been performed in the developed world. Studies of BPA levels in humans living elsewhere in the world are still needed.

7.3.2. BPA levels in the environment

At this time, it is unknown which sources of BPA exposure contribute at which levels to the total exposure levels. For this reason, the most appropriate route(s) of exposure have still not been determined.

7.3.3. Epidemiology studies of human exposures

At this time, the total number of studies examining BPA and human disorders and diseases is very small. Many more studies are needed to investigate the relationship between BPA exposure and other health issues. It has been proposed that xenoestrogens such as BPA could possibly play a role in reproductive cancers (testicular, prostate, breast, uterine, ovarian, etc.), fertility problems (low sperm count, decreased sperm quality), and other endocrine related endpoints. There are potential problems with answering these questions, including the likelihood that most humans are exposed to many different xenoestrogens, antiestrogens, and other endocrine disruptors. To date, very few animal studies have examined xenoestrogen mixtures. Therefore, it remains unknown how the mechanistic actions of BPA are altered by combinations of other estrogenic chemicals. Methods are needed to separate the effects of multiple endocrine disrupting chemicals, and additional methods are needed to better examine chemical mixtures. It is also unknown how BPA interacts with endogenous estrogens. Markers of total xenoestrogen burden and biomarkers specific to BPA are needed.

Although providing interesting preliminary data on potential health risks, the available epidemiology studies have many limitations. Overall, the studies have small sample sizes, limited details on subject selection criteria, and they generally are cross-sectional designs that include limited control for potential confounders. These limitations in design contribute to the limited ability to make conclusions based on the epidemiology of potential health risks of BPA. Finally, due to their design, it was not possible to determine whether altered BPA metabolism is a secondary effect due to the dysfunctions and conditions examined in these studies.

There is limited evidence that BPA levels/concentrations vary between men and women and/or with several endocrine-related syndromes and diseases, including polycystic ovarian syndrome and obesity. However, no conclusions can be made from these studies.

7.3.4. BPA metabolism in humans and animals

Estimates in the literature of BPA intake have been made using urinary outputs. These estimates require assumptions based on steady state excretion. Additional studies and subsequent excretion models are needed to compare single urine collections with total excretions all day long.

At this time, we are not aware of any studies that have examined BPA pharmacokinetics in animal models following continuous low-level exposures. Research is needed to better mimic the current exposure of humans to BPA, and continuous exposure studies are needed in both pregnant and non-pregnant animals.

In humans, both acute metabolic studies and continuous exposure studies are needed. While differences in metabolism are suspected between humans and rodent models, the lack of acute metabolic studies in humans with acceptable measurement capabilities has prevented this hypothesis from being furthered. However, the possibility of adverse effects from exposure to BPA particularly during fetal development limits the kind of research that can be performed. The ability to measure BPA levels in serum and other bodily fluids suggest that either intake is much higher than accounted for, or that BPA can bioaccumulate in some conditions such as pregnancy, or both. Research using both animal models and human subjects, as well as epidemiology studies, are needed to address these hypotheses.

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