HUMAN EXPOSURE TO BISPHENOL A (BPA)

Laura N. Vandenberg[1], Russ Hauser[2], Michele Marcus[3], Nicolas Olea[4], and Wade V. Welshons[5]

[1]Tufts University Sackler School of Graduate Biomedical Sciences, Boston MA 02111
[2]Department of Environmental Health, Harvard School of Public Health, Boston, MA 02115
[3]Emory University, Rollins School of Public Health, Atlanta, GA 30322
[4]Hospital Clinico, University of Granada, 18071 Granada Spain
[5]University of Missouri-Columbia, Department of Biomedical Sciences, Columbia, MO 65211

Corresponding author:
Laura N. Vandenberg
Tufts University School of Medicine
Sackler School of Graduate Biomedical Sciences
136 Harrison Avenue
Boston, MA 02111
laura.vandenberg@tufts.edu
Ph: 617-636-0444
Fax: 617-636-3971

Acknowedgements: The authors gratefully acknowledge expertise and input from additional panel members: Jane C. Atkinson, Antonia M. Calafat, Frederick Eichmiller, Albert Kingman, Ruthann Rudel, and Kristina A. Thayer. This review was prepared in conjunction with the Bisphenol A Conference, Chapel Hill, NC, November 28-29, 2006. Support was provided by the National Institute of Environmental Health Sciences and the National Institute of Dental and Craniofacial Research, NIH, DHHS, the W.M. Keck Center for Behavioral Biology at NC State University, and from Commonweal

Running Title: *Human exposure to BPA*

Keywords: serum, urine, epidemiology, disease, epoxy resins, dental sealants, polycarbonate plastic, metabolism

Abbreviations

BADGE	bisphenol A diglycidyl ether
Bis-DMA	bisphenol A dimethylacrylate
BPA	bisphenol A
BPA-gluc	bisphenol A glucuronide
°C	degrees Celsius
CDC	Centers 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

Introduction

The plastic monomer and plasticizer bisphenol A (BPA) is one of the highest volume chemicals produced worldwide, with over 6 million 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*, and appear to be within an order of magnitude of the levels of BPA in animal studies; 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 [3,4,5]. The affinity of BPA for ERs is 10,000 to 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- to 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 [6]) in addition to effects initiated by binding of BPA to the classical nuclear or genomic estrogen receptors. The accompanying review from this meeting on Molecular Mechanisms of BPA Action describes recent findings showing 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 nongenomic and

involve membrane-associated forms of the estrogen receptors. The relevance of these mechanisms to the in vivo situation are discussed in that panel review as well.

"Low-doses" of endocrine disrupting chemicals were defined by the NIEHS Low Dose Peer Review as doses below the accepted NOAEL for the chemical [7], 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 the In vivo panel report.; over 40 of these are below the RfD for BPA of 50 micrograms/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 [8,9,10,11]. 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 [12,13,14].

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.

1. 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.

Serum, blood & plasma

Since 1999 [15], 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 0.2–20 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– 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 [16] 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 [17], and 2) BPA action in cell cultures have been reported in the low picogram to low nanogram per

milliliter range (see [6] and Molecular Mechanisms panel report). 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 [18], 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 the serum from pregnant women, umbilical cord blood, and fetal plasma [19,20,21,22]. The results from these studies (Table 1) indicate that BPA crosses the maternal-fetal placental barrier. In one report [19], the human maternal sera showed average BPA at 1.4 –2.4 ng/ml levels, whereas the 15- to 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 [23]. Additionally, results from this study and another from the same group [24] 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 [25]. However, the implications of the human studies are limited by their small sample sizes.

Pregnancy-associated fluids

Several investigators have measured BPA levels in placental tissue and amniotic fluid [19,20,21,26] (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 [19]. The authors of this study proposed that BPA may accumulate in early fetuses due to a lower metabolic clearance of 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 [21] 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 [20]. 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.

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. 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 0.61ng/ml [27]. In a study of a similar size (n=20), using HPLC coupled with isotope-dilution tandem MS, Ye et al. 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 [28].

Another study of interest reported BPA concentrations in human colostrum, breast milk produced within the first three days after giving birth [29,30]. 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 1-7ng/ml and a mean level of 3.41ng/ml. It is uncertain if this higher concentration in colostrum compared to breast milk collected more than one week after delivery is due to differences in the detection method (HPLC-FD vs ELISA), or whether there are changes in BPA metabolism during the period of lactation.

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 Centers 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 [31]. 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 [32].

Another study also examined sex differences in urinary BPA levels in 30 Korean adults by HPLC with fluorescence detection [33]. 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 vs 1.00 ng/ml) while women had significantly higher levels of BPA-sulfate (1.20 vs 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 & Watanabe, 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 micrograms/day [34]. Additionally, Matsumoto et al. postulated that Japanese University students (50 in 1992 and 56 in 1999) may be exposed to levels of BPA resulting in 10 micrograms/g creatine [35] 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.

Semen & follicular fluid

A limited number of studies have examined BPA levels in other bodily fluids such as follicular fluid [19] and semen [36,37]. BPA levels measured in follicular fluid by ELISA showed an average of 2.0 ng/ml [19]. 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 [38].

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 [36]. 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 [36]. In another study, Katayama and colleagues 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 of followed by HPLC with capillary electrophoresis (LOD: 1 picogram/ml) [37]. Therefore, it appears unlikely that BPA is present in human semen samples considering the high sensitivities of the assays used.

2. 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.

Sources and estimates of BPA exposure

Two studies have been conducted to estimate BPA exposure levels in young children. The first involved just 9 children and was designed to examine their potential exposures at home and in daycare [39]. 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 per day. A second observational study performed by the same group of investigators examined BPA exposures in 257 preschool children [40]. 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 per day, and estimated inhalation exposure was 0.24-0.41 ng/kg per 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) [41]. Urinary BPA levels were significantly higher in 42 men exposed occupationally than in 42 non-exposed workers.

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 [23,24]. A negative correlation between BPA and FSH was found among men in the study of epoxy resin workers described above [41] 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 [21]. 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 [42]; 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 nonparous 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 [43].

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.

3. 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 microgram/kg body weight/day [44]. Alternatively, the European Commission's Scientific Committee on Food [45] estimated BPA exposure to be 0.48-1.6 micrograms/kg body weight/day from food sources, while Thomson et al. estimated that New Zealanders consume as much as 4.8 micrograms/day from dietary sources alone [46].

BPA from plastics, baby bottles & other consumer products

In 1993, Krishnan et al. found that autoclaving cell culture media in polycarbonate flasks led to the release of an unknown estrogenic substance [47]. Using NMR and mass spectrometry, it was determined that the flasks were leaching BPA. At that time, Krishnan and colleagues 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 [48]. Different results have been obtained from various groups studying the effects of washing, boiling, and brushing on BPA leaching. Sun et al. found that BPA leached from polycarbonate bottles, but not glass bottles, on their first use [49]. 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 [50,50]. 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 [48]; these calculations estimated that newborns, because of their lower body weight, are exposed to the highest levels of BPA (24

micrograms/kg body weight/day). By 3 months of age, dietary exposure estimates drop to 15 micrograms/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. examined the composition of a microwavable polycarbonate plastic container [51]. BPA was found in the plastic at a concentration of 30 microgram/g plastic and the potential migration level was estimated at 6.5 microgram/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 [52]. An examination of 5 polyvinyl chloride stretch films indicated measurable BPA content in 4 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 5 films showed leaching into water and acetic acid, while 4 of 5 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 twenty 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 [53]. In contrast, paper towels made from recycled paper had BPA levels ranging from 0.55-24.1 mg/kg. In a second study examining 28 paper products in food-contact use, 67% of the twelve products made from recycled paper contained BPA at a range of 0.19-26 mg/kg [54]. Of the 16 products made from virgin paper, thirteen 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 [55]. 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.

Leaching of BPA from food cans & 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 microgram of BPA per can [56]. Kang et al. conducted a comprehensive study and found that heating temperature had a significant effect on BPA migration, to a greater extent than heating time [57]. 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 [58]. 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: 18.2x) 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 [59], vegetables [56,60,61] and fish [61,62]. Others have found BPA contamination in infant formula [63,64]. Thomson et al. used information available from the literature to estimate total dietary estrogen exposures for New Zealand population subgroups [46]. 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 micrograms/day.

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 conversion 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. applied approximately 50mg total of sealant to 12 molars [65]. Total saliva was collected continuously for one entire hour before and one entire hour after the application procedure. After the treatment, all samples were found to contain variable amounts of BPA, ranging from 3.3 to 30.0 micrograms/ml saliva. Subsequent studies, using different composite applications and saliva collection techniques, have added some controversy to this topic. Arenholt-Bindslev et al. applied 38mg of fissure sealant to 4 molars in 8 volunteers and found detectable levels of BPA in small saliva samples taken immediately after placement of the sealant [66]. However, no BPA was detected in samples collected at 1 hour or 24 hours after sealant application. Fung et al., however, detected BPA in some saliva samples of dental patients collected at 1 and 3 hours after the application of dental materials [67]. 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. collected saliva samples from 8 patients undergoing dental procedures and found BPA in all specimens [68]. BPA levels ranged from 15.3 to 32.4 ng/ml. Sasaki et al. used an ELISA method to detect BPA in saliva samples from 21 patients treated with one of 9 commercially available dental resins [69]. BPA was detected in saliva at several tens to 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. examined BPA in urine and saliva of 14 adults treated with one of two different dental sealants [70]. Saliva samples were collected before, immediately after, and 1 hour after sealant application. Urine samples were collected before and at 1 and 24 hours 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 hour 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 [66,71,72,73,69,70] while other studies have been unable to detect BPA in either dental sealants or eluates [74,75,76]. Additionally, the storage of saliva samples can affect the detection of BPA [77]. Saliva samples were spiked with BPA, BPA dimethylacrylate (Bis-DMA), or triethylene glycol dimethacrylate (TEGDMA). The samples were stored at –20 °C or –70 °C, and then tested by HPLC and GC-MS (LOD: 1ng/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.

Sewage leachates and water

Several studies have demonstrated that BPA can be detected in landfill leachates (Table 5). Kawagoshi and colleagues 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 [78]. 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 [79], in the upper range of levels detected in Japan [80]. 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 [79]. 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 [81].

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 [82]. Using an extraction derivation reaction to convert contaminants into their pentaflouorobenzoylate esters followed by GC-MS, Kuch and Ballschmiter achieved an LOD of 20 picograms per liter 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 [83]. 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 [84]. This study found a median level of detection of 0.14 micrograms per liter, and a maximum measure of 12 micrograms per liter.

Air & 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 [85].

In a survey of 120 homes for the presence of endocrine disrupting chemicals, Rudel et al. found BPA present in 86% of house dust samples at concentrations ranging from 0.2-17.6 micrograms/gram [86]. Another study from the same group found BPA in 3 of 6 residential and office dust samples [87]. 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 [85]. 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.

4. BPA metabolism in humans & 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 [31,70]. 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 [88,89]. 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 [31,32]. 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 [90], and the pharmacokinetics of BPA based on adult oral exposure can not 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.

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 the BPA conjugates has been reported as very low to none [91,88,92], 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; 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 the In Vivo Panel Report) will be compared to the adult animal metabolic studies of oral exposure 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 the In Vitro Panel Report).

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 after 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 [17]. 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 [17]. 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 [93], 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 h 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 [93] or in other studies at low oral doses [94,95,17] 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 [89]). 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 [96].

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 nonpregnant and pregnant adults [97], only slight increases in circulating BPA following one exposure compared to multiple exposures [98], 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 nonpregnant 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 (see In Vitro panel report).

As indicated above, the USEPA reference dose for BPA is currently 50 µg/kg/d. As detailed in the report from the In Vivo panel, there are over 40 studies reporting effects at or below this RfD. 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 [88,99,100,93,101] 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 Figure 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 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 Figure 1 are presented in Figure 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, B and C); publications report proportionality with dose where encountered [88,99,100,93,101]. 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, F and G) to address pooling the small set of pregnant animal data with the larger set of nonpregnant animal data; the conclusion of at least one report is that the pharmacokinetics do not vary between nonpregnant and pregnant rodents [100].

Figure 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, B and 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 nonpregnant 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. [100] that BPA metabolism does not differ significantly between pregnant and non-pregnant females.

The data in Figure 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 Figure 1, at 1 hr after oral BPA administration, the blood levels of unconjugated BPA ranged from 0.003 - 0.3 ng/ml. At 24 h the values ranged from 0.002 - 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 (See In Vivo

panel report) 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 [89], 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 hour after administration of 50 µg/kg, rodent blood levels are over 10-fold below median human blood levels, and to achieve these levels human would have to be exposed to a dose greater than 500 µg/kg. If human metabolism and clearance is more rapid than rodent clearance, which is concluded by studies which have addressed the issue [102,103,89], then the human exposure to achieve the current human circulating levels would have to be well above 500 µg/kg/day (well above 32 mg/day/adult considering a 65 kg human). This is consistent with the observation of Shin at al. [98] that 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 & Tsutsumi [23]. 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) (see In Vitro Panel Report) median 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 In Vitro and In Vivo panel reports).

Comparisons of human exposure levels & 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 (Zalko, 2003;

Kurebayashi, 2005). 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 differences 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 [104,43], studies using larger and more widespread populations are needed.

Animal models of BPA metabolism- digestion & 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 radiolabelled BPA/kg body weight either by oral or intravenous (i.v.) exposure [95,95]. 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 hours of treatment. Fecal excretion from the i.v. and oral dosing was 77.6 and 81.6% of the administered dose, respectively. Collectively, Kurebayashi and colleagues 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. identified and examined UGT2B1, a liver enzyme responsible for glucuronidation of BPA and other xenoestrogens [105]. 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 [106]. 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 [107]. 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 the treatment with a high dose (100 micromolar). 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 [108,107]. These authors also suggest that the effects of BPA may be enhanced by repeated, continuous exposure [108].

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 examined oral administration of 1 g BPA/kg to pregnant rats on day 18 of gestation [109]. BPA was detected in maternal blood within 10 minutes of dosing (2.89

microgram/g), reached a peak concentration at 20 minutes after dosing (14.7 microgram/g) and gradually decreased over a period of 10 hours. BPA was also detected in fetuses within 10 minutes of dosing (2.00 microgram/g); a maximum concentration was reached at 20 minutes (9.22 microgram/g) and levels gradually decreased with time. The concentration after 6 hours 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 minutes (mice) and 1 hour (monkeys) of treatment [110].

Zalko et al. demonstrated in a mouse model that much lower doses (25 microgram/kg) of BPA were also able to cross the placental barrier [17]. 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).

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 and colleagues administered 5 mg radioactive BPA/person (54-90 micrograms/kg body weight) and report that elimination of BPA was complete within 24 hours of dosing [102,102]. Maximal plasma concentrations were reached 80 minutes after dosing and rapidly declined for the next 6 hours. 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 [105,105].

In another metabolic study, BPA was administered (25 micrograms/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-gluc) [103]. In the three men examined, 85% of the applied BPA dose was recovered in urine after 5 hours, 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 [33,31,31,33]. 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 4 individuals [103], 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 [111]. Alternatively, Pritchett et al. 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 [112]. Additional studies are needed to rectify these theories. In the studies of Yoshihara and colleagues discussed above, rat liver extracts were found to produce a BPA metabolite with increased estrogenic activity [106]. 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 [89]. 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.

5. 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 microgram/kg/day to almost 5 micrograms/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 and colleagues 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 (Welshons, 2006).

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.

Conclusions and Levels of Confidence for Different Outcomes

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

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 to 4.4 ng/ml range (1 to 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 to 3 ng/ml range (4 to 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.

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.

BPA metabolism in humans & 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.

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

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 microgram/kg/day to almost 5 micrograms/kg/day. More studies and mathematical models of potential exposures are needed, particularly because many environmental sources of BPA exposure have been identified.

BPA metabolism in humans & 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.

C. Research to be pursued in future scientific investigations:

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.

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.

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, anti-estrogens, 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.

BPA metabolism in humans & 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 the 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 nonpregnant 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.

Acknowledgements

The authors gratefully acknowledge expertise and input from additional panel members: Jane C. Atkinson, Antonia M. Calafat, Frederick Eichmiller, Albert Kingman, Ruthann Rudel, and Kristina A. Thayer. This review was prepared in conjunction with the Bisphenol A Conference, Chapel Hill, NC, November 28-29, 2006. Support was provided by the National Institute of Environmental Health Sciences and the National Institute of Dental and Craniofacial Research, NIH, DHHS, the W.M. Keck Center for Behavioral Biology at NC State University, and from Commonweal.

References

[1] Burridge E. Bisphenol A: product profile. Eur Chem News. 2003;April:14-20.

[2] www.bisphenol-a.org 2007.

[3] Gould JC, Leonard LS, Maness SC et al. Bisphenol A interacts with the estrogen receptor α in a distinct manner from estradiol. Mol Cell Endocrinol. 1998;142:203-14.

[4] Kuiper GG, Lemmen JG, Carlsson B et al. Interaction of estrogenic chemicals and phytoestrogens with estrogen receptor beta. Endocrinology. 1998;139:4252-63.

[5] Pennie WD, Aldridge TC, Brooks AN. Differential activation by xenoestrogens of ER α and ER β when linked to different response elements. J Endocrinol. 1998;158:R11-R14.

[6] Welshons WV, Nagel SC, vom Saal FS. Large effects from small exposures. III. Endocrine mechanisms mediating effects of bisphenol A at levels of human exposure. Endocrinology. 2006;147:S56-S69.

[7] EDSTAC. Endocrine Disruptor Screening and Testing Advisory Committee Final Report. Washington, D.C.: US Environmental Protection Agency; 1998.

[8] Colerangle JB, Roy D. Profound effects of the weak environmental estrogen-like chemical bisphenol A on the growth of the mammary gland of Noble rats. J Steroid Biochem Molec Biol. 1997;60:153-60.

[9] Steinmetz R, Brown NG, Allen DL, Bigsby RM, Ben-Jonathan N. The environmental estrogen bisphenol A stimulates prolactin release in vitro and in vivo. Endocrinology. 1997;138:1780-6.

[10] Steinmetz R, Mitchner NA, Grant A, Allen DL, Bigsby RM, Ben-Jonathan N. The xenoestrogen bisphenol A induces growth, differentiation, and c-*fos* gene expression in the female reproductive tract. Endocrinology. 1998;139:2741-7.

[11] Markey CM, Michaelson CL, Veson EC, Sonnenschein C, Soto AM. The mouse uterotropic assay: a re-evaluation of its validity in assessing the estrogenicity of bisphenol A. Environ Health Perspect. 2001;109:55-60.

[12] Sharpe RM, Skakkebaek NE. Are oestrogens involved in falling sperm count and disorders of the male reproductive tract? Lancet. 1993;341:1392-5.

[13] Skakkebaek NE, Meyts ER, Jorgensen N et al. Germ cell cancer and disorders of spermatogenesis: an environmental connection? APMIS. 1998;106:3-12.

[14] Munoz de Toro MM, Markey CM, Wadia PR et al. Perinatal exposure to Bisphenol A alters peripubertal mammary gland development in mice. Endocrinology. 2005;146:4138-47.

[15] Sajiki J, Takahashi K, Yonekubo J. Sensitive method for the determination of bisphenol-A in serum using two systems of high-performance liquid chromatography. Journal of Chromatography B. 1999;736:255-61.

[16] Fukata H, Miyagawa H, Yamazaki N, Mori C. Comparison of ELISA- and LC-MS-Based Methodologies for the Exposure Assessment of Bisphenol A. Toxicology Mechanisms & Methods. 2006;16:427-30.

[17] Zalko D, Soto AM, Dolo L et al. Biotransformations of bisphenol A in a mammalian model: answers and new questions raised by low-dose metabolic fate studies in pregnant CD1 mice. Environ Health Perspect. 2003;111:309-19.

[18] Inoue K, Kato K, Yoshimura Y, Makino T, Nakazawa H. Determination of bisphenol A in human serum by high-performance liquid chromatography with multi-electrode electrochemical detection. Journal of Chromatography B. 2000;749:17-23.

[19] Ikezuki Y, Tsutsumi O, Takai Y, Kamei Y, Taketani Y. Determination of bisphenol A concentrations in human biological fluids reveals significant early prenatal exposure. Hum Reprod. 2002;17:2839-41.

[20] Schonfelder G, Wittfoht W, Hopp H, Talsness CE, Paul M, Chahoud I. Parent bisphenol A accumulation in the human maternal-fetal-placental unit. Environ Health Perspect. 2002;110:A703-A707.

[21] Yamada H, Furuta I, Kato EH et al. Maternal serum and amniotic fluid bisphenol A concentrations in the early second trimester. Reproductive Toxicology. 2002;16:735-9.

[22] Tan BLL, Ali Mohd M. Analysis of selected pesticides and alkylphenols in human cord blood by gas chromatograph-mass spectrometer. Talanta. 2003;61:385-91.

[23] Takeuchi T, Tsutsumi O. Serum bisphenol A concentrations showed gender differences, possibly linked to androgen levels. Biochem Biophys Res Commun. 2002;291:76-8.

[24] Takeuchi T, Tsutsumi O, Ikezuki Y, Takai Y, Taketani Y. Positive relationship between androgen and the endocrine disruptor, bisphenol A, in normal women and women with ovarian dysfunction. Endocrine Journal. 2004;51:165-9.

[25] Takeuchi T, Tsutsumi O, Ikezuki Y et al. Elevated serum bisphenol A levels under hyperandrogenic conditions may be caused by decreased UDP-glucuronosyltransferase activity. Endocrine Journal. 2006;53:485-91.

[26] Engel SM, Levy B, Liu Z, Kaplan D, Wolff MS. Xenobiotic phenols in early pregnancy amniotic fluid. Reproductive Toxicology. 2006;21:110-2.

[27] Sun Y, Irie M, Kishikawa N, Wada M, Kuroda N, Nakashima K. Determination of bisphenol A in human breast milk by HPLC with column-switching and fluorescence detection. Biomed Chromatogr. 2004;18:501-7.

[28] Ye X, Kuklenyik Z, Needham J, Calafat AM. Measuring environmental phenols and chlorinated organic chemicals in breast milk using automated on-line column-switching-high performance liquid chromatography-isotope dilution tandem mass spectrometry. Journal of Chromatography B. 2006;831:110-5.

[29] Kuruto-Niwa R, Tateoka Y, Usuki Y, Nozawa R. Measurement of bisphenol A concentrations in human colostrum. Chemosphere. 2007;66:1160-4.

[30] Kuruto-Niwa R, Tateoka Y, Usuki Y, Nozawa R. Measurement of bisphenol A concentrations in human colostrum. Chemosphere. 2006;

[31] Calafat AM, Kuklenyik Z, Reidy JA, Caudill SP, Ekong J, Needham JL. Urinary concentrations of Bisphenol A and 4-Nonylphenol in a human reference population. Environ Health Perspect. 2005;113:391-5.

[32] Wolff MS, Teitelbaum SL, Windham G et al. Pilot study of urinary biomarkers of phytoestrogens, phthalates, and phenols in girls. Environ Health Perspect. 2007;115:116-21.

[33] Kim Y-H, Kim C-S, Park S, Han SY, Pyo M-Y, Yang M. Gender differences in the levels of bisphenol A metabolites in urine. Biochem Biophys Res Commun. 2003;312:441-8.

[34] Ouichi K, Watanabe S. Measurement of bisphenol A in human urine using liquid chromatography with multi-channel coulometric electrochemical detection. Journal of Chromatography B. 2002;780:365-70.

[35] Matsumoto A, Kunugita N, Kitagawa K et al. Bisphenol A levels in human urine. Environ Health Perspect. 2003;111:101-4.

[36] Inoue K, Wada M, Higuchi T et al. Application of liquid chromatography-mass spectrometry to the quantification of bisphenol A in human semen. Journal of Chromatography B. 2002;773:97-102.

[37] Katayama M, Matsuda Y, Shimokawa K-I, Ishikawa H, Kaneko S. Preliminary monitoring of bisphenol A and nonylphenol in human semen by sensitive high performance liquid chromatography and capillary electrophoresis after proteinase K digestion. Analytical Letters. 2003;36:2659-67.

[38] Hunt PA, Koehler KE, Susiarjo M et al. Bisphenol A exposure causes meiotic aneuploidy in the female mouse. Current Biology. 2003;13:546-53.

[39] Wilson NK, Chuang JC, Lyu C, Menton R, Morgan MK. Aggregate exposures of nine preschool children to persistent organic pollutants at day care and at home. Journal of Exposure Analysis and Environmental Epidemiology. 2003;13:187-202.

[40] Wilson NK, Chuang JC, Morgan MK, Lordo RA, Sheldon LS. An observational study of the potential exposures of preschool children to pentachlorophenol, bisphenol-A, and nonylphenol at home and daycare. Environmental Research. 2007;103:9-20.

[41] Hanaoka T, Nawamura N, Hara K, Tsugane S. Urinary bisphenol A and plasma hormone concentrations in male workers exposed to bisphenol A diglycidyl ether and mixed organic solvents. Occup Environ Med. 2002;59:625-8.

[42] Sugiura-Ogasawara M, Ozaki Y, Sonta S-I, Makino T, Suzumori K. Exposure to bisphenol A is associated with recurrent miscarriage. Hum Reprod. 2005;20:2325-9.

[43] Yang M, Kim S-Y, Chang S-S, Lee I-S, Kawamoto T. Urinary concentrations of bisphenol A in relation to biomarkers of sensitivity and effect and endocrine-related health effects. Environmental and Molecular Mutagenesis. 2006;47:571-8.

[44] Kang J-H, Kondo F, Katayama Y. Human exposure to bisphenol A. Toxicology. 2006;226:79-89.

[45] http://europa.eu.int/comm/food/fs/sc/scf/out128_en.pdf

[46] Thompson BM, Cressey PJ, Shaw IC. Dietary exposure to xenoestrogens in New Zealand. J Environ Monit. 2003;5:229-35.

[47] Krishnan AV, Starhis P, Permuth SF, Tokes L, Feldman D. Bisphenol-A: an estrogenic substance is released from polycarbonate flasks during autoclaving. Endocrinology. 1993;132:2279-86.

[48] Wong KO, Leo LW, Seah HL. Dietary exposure assessment of infants to bisphenol A from the use of polycarbonate baby milk bottles. Food Addit Contam. 2005;22:280-8.

[49] Sun Y, Wada M, Al-Dirbashi O, Kuroda N, Nakazawa H, Nakashima K. High-performance liquid chromatography with peroxyoxalate chemiluminescence detection of bisphenol A migrated from polycarbonate baby bottles using 4-(4,5-diphenyl-1H-imidazol-2-yl)benzoyl chlorine as a label. Journal of Chromatography B. 2000;749:49-56.

[50] Brede C, Fjeldal P, Skjevrak I, Herikstad H. Increased migration levels of bisphenol A from polycarbonate baby bottles after dishwashing, boiling, and brushing. Food Addit Contam. 2003;20:684-9.

[51] Nerín C, Fernandez C, Domeno C, Salafranca J. Determination of potential migrants in polycarbonate containers used for microwave ovens by high-performance liquid chromatography with ultraviolet and fluorescence detection. J Agric Food Chem. 2003;51:5647-53.

[52] Lopez-Cervantes J, Paseiro-Losada P. Determination of bisphenol A in, and its migration from, PVC stretch film used for food packaging. Food Addit Contam. 2003;20:596-606.

[53] Vinggaard AM, Korner W, Lund KH, Bolz U, Petersen JH. Identification and quantification of estrogenic compounds in recycled and virgin paper for household use as determined by an in vitro yeast estrogen screen and chemical analysis. Chem Res Toxicol. 2000;13:1214-22.

[54] Ozaki A, Yamaguchi A, Fujita T, Kuroda K, Endo G. Chemical analysis and genotoxicological safety assessment of paper and paperboard used for food packaging. Food Chem Toxicol. 2004;42:1323-37.

[55] Lopez-Espinosa MJ, Granada A, Araque P et al. Oestrogenicity of paper and cardboard extracts used as food containers. Food Addit Contam. 2007;24:95-102.

[56] Brotons JA, Olea-Serrano MF, Villalobos M, Olea N. Xenoestrogens released from lacquer coating in food cans. Environ Health Perspect. 1994;103:608-12.

[57] Kang J-H, Kito K, Kondo F. Factors influencing the migration of bisphenol A from cans. Journal of Food Protection. 2003;66:1444-7.

[58] Takao Y, Lee HC, Kohra S, Arizono K. Release of bisphenol from food can lining upon heating. Journal of Health Science. 2002;48:331-4.

[59] Kang J-H, Kondo F. Determination of bisphenol A in canned pet foods. Research in Veterinary Science. 2002;73:177-82.

[60] Yoshida T, Horie M, Hoshino Y, Nakazawa H. Determination of bisphenol A in canned vegetables and fruit by high performance liquid chromatography. Food Addit Contam. 2001;18:69-75.

[61] Goodson A, Summerfield W, Cooper I. Survey of bisphenol A and bisphenol F in canned foods. Food Addit Contam. 2002;19:796-802.

[62] Munguía-López EM, Gerardo-Lugo S, Peralta E, Bolumen S, Soto-Valdez H. Migration of bisphenol A (BPA) from can coatings into fatty-food simulant and tuna fish. Food Addit Contam. 2005;22:892-8.

[63] Biles JE, McNeal TP, Begley TH. Determination of bisphenol A migrating from epoxy can coatings to infant formula liquid concentrates. J Agric Food Chem. 1997;45:4697-700.

[64] Kuo H-W, Ding W-H. Trace determination of bisphenol A and phytoestrogens in infant formula powders by gas chromatography-mass spectrometry. Journal of Chromatography A. 2004;1027:67-74.

[65] Olea N, Pulgar R, Perez P et al. Estrogenicity of resin-based composites and sealants used in dentistry. Environ Health Perspect. 1996;104(3):298-305.

[66] Arenholt-Bindselv D, Breinholt V, Preiss A, Schmalz G. Time-related bisphenol-A content and estrogenic activity in saliva samples collected in relation to placement of fissure sealants. Clin Oral Invest. 1999;3:120-5.

[67] Fung EYK, Ewoldsen NO, St.Germain JrHA et al. Pharmacokinetics of bisphenol A released from a dental sealant. J Am Dent Assoc. 2000;131:51-8.

[68] Zafra A, del Olmo M, Pulgar R, Navalón A, Vílchez JL. Determination of bisphenol-A and related compounds in human saliva by gas chromatography-mass spectometry. Chromatographia. 2002;56:213-8.

[69] Sasaki N, Okuda K, Kato T et al. Salivary bisphenol-A levels detected by ELISA after restoration with composite resin. Journal of Materials Science: Materials in Medicine. 2005;16:297-300.

[70] Joskow R, Barr DB, Barr JR, Calafat AM, Needham LL, Rubin C. Exposure to bisphenol A from bis-glycidyl dimethacrylate-based dental sealants. J Am Dent Assoc. 2006;137:353-62.

[71] Lewis JB, Rueggeberg FA, Lapp CA, Ergle JW, Schuster GS. Identification and characterization of estrogen-like components in commercial resin-based dental restorative materials. Clin Oral Invest. 1999;3:107-13.

[72] Schmalz G, Preiss A, Arenholt-Bindselv D. Bisphenol-A content of resin monomers and related degradation products. Clinical Oral Investigations. 1999;3:114-9.

[73] Pulgar R, Olea-Serrano F, Novillo-Fertrell A et al. Determination of bisphenol A and related aromatic compounds released from Bis-GMA-based composites and sealants by high performance liquid chromatography. Environ Health Perspect. 2000;108:21-7.

[74] Nathanson D, Lertpitayakun P, Lamkin MS, Edalatpour M, Chou LL. In vitro elution of leachable components from dental sealants. J Am Dent Assoc. 1997;128:1517-23.

[75] Tarumi H, Imazato S, Narimatsu M, Matsuo M, Ebisu S. Estrogenicity of fissure sealants and adhesive resins determined by reporter gene assay. J Dent Res. 2000;79:1838-43.

[76] Wada H, Tarumi H, Imazato S, Narimatsu M, Ebisu S. *In vitro* estrogenicity of resin composites. J Dent Res. 2004;83:222-3.

[77] Atkinson JC, Diamond F, Eichmiller F, Selwitz R, Jones G. Stability of bisphenol A, triethylene-glycol dimethyacrylate, and bisphenol A dimethyacrylate in whole saliva. Dental Materials. 2002;18:128-35.

[78] Kawagoshi Y, Fujita Y, Kishi I, Fukunaga I. Estrogenic chemicals and estrogenic activity in leachate from municipal waste landfill determined by yeast two-hybrid assay. J Environ Monit. 2003;5:269-74.

[79] Coors A, Jones PD, Giesy JP, Ratte HT. Removal of estrogenic activity from municipal waste landfill leachate assessed with a bioassay based on reporter gene expression. Environ Sci Technol. 2003;37:3430-4.

[80] Yamamoto T, Yasuhara A, Shiraishi H, Nakasugi O. Bisphenol A in hazardous waste landfill leachates. Chemosphere. 2001;42:415-8.

[81] www.ecologycenter.org/iptf/recycling/index.html 2007.

[82] Kuch HM, Ballschmiter K. Determination of endocrine-disrupting phenolic compounds and estrogens in surface and drinking water by HRGC-(NCI)-MS in the picogram per liter range. Environ Sci Technol. 2001;35:3201-6.

[83] Belfroid A, van Velzen M, van der Horst B, Vethaak D. Occurrence of bisphenol A in surface water and uptake in fish: evaluation of field measurements. Chemosphere. 2002;49:97-103.

[84] Kolpin DW, Furlong ET, Meyer MT et al. Pharmaceuticals, hormones, and other organic wastewater contaminants in U.S. streams, 1999-2000: A national reconnaissance. Environ Sci Technol. 2002;36:1202-11.

[85] Matsumoto H, Adachi S, Suzuki Y. Bisphenol A in ambient air particulates responsible for the proliferation of MCF-7 human breast cancer cells and its concentration changes over 6 months. Arch Environ Con Tox. 2005;48:459-66.

[86] Rudel RA, Camann DE, Spengler JD, Korn LR, Brody JG. Phthalates, alkylphenols, pesticides, polybrominated diphenyl ethers, and other endocrine-disrupting compounds in indoor air and dust. Environ Sci Technol. 2003;37:4543-55.

[87] Rudel RA, Brody JG, Spengler JD et al. Identification of selected hormonally active agents and animal mammary carcinogenesis in commercial and residential air and dust samples. Journal of the Air and Waste Management Association. 2001;51:499-513.

[88] Pottenger LH, Domoradzki JY, Markham DA, Hansen SC, Cagen SZ, Waechter JMJr. The relative bioavailability and metabolism of bisphenol A in rats is dependent upon the route of administration. Toxicol Sci. 2000;54:3-18.

[89] Teeguarden JG, Waechter JMJr, Clewell HJ, Covington TR, Barton HA. Evaluation of oral and intravenous route pharmacokinetics, plasma binding protein, and uterine tissue dose metrics of bisphenol A: a physiologically based pharmacokinetic approach. Toxicol Sci. 2005;85:823-38.

[90] Matsumoto J, Yokota H, Yuasa A. Developmental increases in rat hepatic microsomal UDP-glucuronosyltransferase activities toward xenoestrogens and decreases during pregnancy. Environ Health Perspect. 2002;110:193-6.

[91] Snyder RW, Maness SC, Gaido KW, Sumner SCJ, Fennell TR. Metabolism and disposition of Bisphenol A in female rats. Toxicol Appl Pharmacol. 2000;168:225-34.

[92] Matthews JB, Twomey K, Zacharewski TR. In vitro and in vivo interactions of bisphenol A and its metabolite, bisphenol A glucuronide, with estrogen receptors alpha and beta. Chem Res Toxicol. 2001;14:149-57.

[93] Kurebayashi H, Nagatsuka S, Nemoto H, Noquchi H, Ohno Y. Disposition of low doses of 14C-bisphenol A in male, female, pregnant, fetal, and neonatal rats. Arch Toxicol. 2005;79:243-52.

[94] Kurebayashi H, Harada R, Stewart RK, Numata H, Ohno Y. Disposition of a low dose of bisphenol A in male and female cynomolgus monkeys. Toxicol Sci. 2002;68:32-42.

[95] Kurebayashi H, Betsui H, Ohno Y. Disposition of a low dose of ^{14}C-bisphenol A in male rats and its main biliary excretion as BPA glucuronide. Toxicol Sci. 2003;73:17-25.

[96] Nagel SC, vom Saal FS, Thayer KA, Dhar MG, Boechler M, Welshons WV. Relative binding affinity-serum modified access (RBA-SMA) assay predicts the relative *in vivo* bioactivity of the xenoestrogens bisphenol A and octylphenol. Environ Health Perspect. 1997;105:70-6.

[97] Domoradzki JY, Pottenger LH, Thornton CM et al. Metabolism and pharmacokinetics of bisphenol A (BPA) and the embryo-fetal distribution of BPA and BPA-monoglucuronide in CD Sprague-Dawley rats at three gestational stages. Toxicol Sci. 2003;76:21-34.

[98] Shin BS, Kim CH, Jun YS et al. Physiologically based pharmacokinetics of bisphenol A. J Toxicol Environ Health A. 2004;67:1971-85.

[99] Upmeier A, Degan GH, Diel P, Michna H, Bolt HM. Toxicokinetics of bisphenol A in female DA/Han rats after a single i.v. and oral administration. Toxiokinetics and Metabolism. 2000;74:431-6.

[100] Domoradzki JY, Thornton CM, Pottenger LH et al. Age and dose dependency of the pharmacokinetics and metabolism of bisphenol A in neonatal Sprague-Dawley rats following oral administration. Toxicol Sci. 2004;77:230-42.

[101] Tominaga T, Negishi T, Hirooka H et al. Toxicokinetics of bisphenol A in rats, monkeys and chimpanzees by the LC-MS/MS method. Toxicology. 2006;226:208-17.

[102] Volkel W, Colnot T, Csanady GA, Filser JG, Dekant W. Metabolism and kinetics of bisphenol A in humans at low doses following oral administration. Chem Res Toxicol. 2002;15:1281-7.

[103] Volkel W, Bittner N, Dekant W. Quantitation of bisphenol A and bisphenol A glucuronide in biological samples by high performance liquid chromatography-tandem mass spectrometry. Drug Metabolism and Disposition. 2005;33:1748-57.

[104] Yang M, Kim S-Y, Lee S-M et al. Biological monitoring of bisphenol A in a Korean population. Arch Environ Contam Toxicol. 2003;44:546-51.

[105] Yokota H, Iwano H, Endo M et al. Glucuonidation of the environmental oestrogen bisphenol A by an isoform of UDP-glucuronosyltransferase, UGT2B1, in the rat liver. Biochem J. 1999;340:405-9.

[106] Yoshihara S, Mizutare T, Makishima M et al. Potent estrogenic metabolites of bisphenol A and bisphenol B formed by rat liver S9 fraction: their structures and estrogenic potency. Toxicol Sci. 2004;78:50-9.

[107] Inoue K, Murayama S, Takeba K, Yoshimura Y, Nakazawa H. Contamination of xenoestrogens bisphenol A and F in honey: safety assessment and analytical method of these compounds in honey. Journal of Food Composition and Analysis. 2003;16:497-506.

[108] Sakamoto H, Yokota H, Kibe R, Sayama Y, Yuasa A. Excretion of bisphenol A-glucuronide into the small intestine and deconjugation in the cecum of the rat. Biochemica et Biophysica Acta. 2002;1573:171-6.

[109] Takahashi O, Oishi S. Disposition of orally administered 2,2-bis(4-hydroxyphenyl) propane (Bisphenol A) in pregnant rats and placental transfer to fetuses. Environ Health Perspect. 2000;108:931-5.

[110] Uchida K, Suzuki A, Kobayashi Y et al. Bisphenol A administration during pregnancy results in fetal exposure in mice and monkeys. Journal of Health Science. 2002;48:579-82.

[111] Elsby R, Maggs JL, Ashby J, Park BK. Comparison of the modulatory effects of human and rat liver microsomal metabolism on the estrogenicity of bisphenol A: implications for extrapolation to humans. J Pharmacol Exp Ther. 2001;297:103-13.

[112] Pritchett JJ, Kuester RK, Sipes IG. Metabolism of bisphenol a in primary cultured hepatocytes from mice, rats, and humans. Drug Metabolism and Disposition. 2002;30:1180-5.

[113] Inoue K, Yamaguchi A, Wada M, Yoshimura Y, Makino T, Nakazawa H. Quantitative detection of bisphenol A and bisphenol A diglycidyl ether metabolites in human plasma by liquid chromatography-electrospray mass spectrometry. Journal of Chromatography B. 2001;765:121-6.

[114] Todaka E, Mori C. Necessity to establish new risk assessment and risk communication for human fetal exposure to multiple endocrine disruptors in Japan. Congenital Anomalies. 2002;42:87-93.

[115] Kuroda N, Kinoshita Y, Sun Y et al. Measurement of bisphenol A levels in human blood serum and acitic fluid by HPLC using a fluorescent labeling reagent. Journal of Pharmaceutical and Biomedical Analysis. 2003;30:1743-9.

[116] Otaka H, Yasuhara A, Morita M. Determination of bisphenol A and 4-nonlyphenol in human milk using alkaline digestion and cleanup by solid-phase extraction. Analytical Sciences. 2003;19:1663-6.

[117] Hiroi H, Tsutsumi O, Takeuchi T et al. Differences in serum bisphenol A concentrations in premenopausal normal women and women with endometrial hyperplasia. Endocrine Journal. 2004;51:595-600.

[118] Brock JW, Yoshimura Y, Barr JR et al. Measurement of bisphenol A levels in human urine. Journal of Exposure Analysis and Environmental Epidemiology. 2001;11:323-8.

[119] Tsukioka T, Brock J, Graiser S, Nguyen J, Nakazawa H, Makino T. Determination of trace amounts of Bisphenol A in urine by negative-ion-chemical-ionization-gas chromatography/mass spectrometry. Analytical Sciences. 2003;19:151-3.

[120] Liu Z, Wolff MS, Moline J. Analysis of environmental biomarkers in urine using an electrochemical detector. Journal of Chromatography B. 2005;819:155-9.

[121] Ye X, Kuklenyik Z, Needham LL, Calafat AM. Quantification of urinary conjugates of bisphenol A, 2,5-dichlorophenol, and 2-hydroxy-4-methoxybenzophenone in humans by online solid phase extraction-high performance liquid chromatography-tandem mass spectrometry. Anal Bioanal Chem. 2005;383:638-44.

[122] Mountfort KA, Kelly KA, Jickells SM, Castle L. Investigations into the potential degradation of polycarbonate baby bottles during sterilization with consequent release of bisphenol A. Food Addit Contam. 1997;14:737-40.

[123] D'Antuono A, Dall'Orto VC, Lo Balbo A, Sobral S, Rezzano I. Determination of bisphenol A in food-stimulating liquids using LCED with a chemically modified electrode. J Agric Food Chem. 2001;49:1098-101.

[124] Sajiki J, Yonekubo J. Leaching of bisphenol A (BPA) to seawater from polycarbonate plastic and its degradation by reactive oxygen species. Chemosphere. 2003;51:55-62.

[125] Sajiki J, Yonekubo J. Leaching of bisphenol A (BPA) from polycarbonate plastic to water containing amino acids and its degradation by radical oxygen species. Chemosphere. 2004;55:861-7.

[126] Bae B, Joeng JH, Lee SJ. The quantification and characterization of endocrine disruptor bisphenol-A leaching from epoxy resin. Water Science and Technology. 2002;46:381-7.

[127] Kang J-H, Kondo F. Bisphenol A migration from cans containing coffee and caffeine. Food Addit Contam. 2002;19:886-90.

[128] Biles JE, McNeal TP, Begley TH, Hollifield HC. Determination of Bisphenol-A in reusable polycarbonate food-contact plastics and migration to food simulating liquids. J Agric Food Chem. 1997;45:3541-4.

[129] Howe SR, Borodinsky L. Potential exposure to bisphenol A from food-contact use of polycarbonate resins. Food Addit Contam. 1998;15:370-5.

[130] Munguía-López EM, Peralta E, Gonzalez-Leon A, Vargas-Requena C, Soto-Valdez H. Migration of bisphenol A (BPA) from epoxy can coatings to Jalapeño peppers and an acid food simulant. J Agric Food Chem. 2002;50:7299-302.

[131] Maragou NC, Lampi EN, Thomaidis NS, Koupparis MA. Determination of bisphenol A in milk by solid phase extraction and liquid chromatography-mass spectrometry. Journal of Chromatography A. 2006;1129:165-73.

[132] Noda M, Komatsu H, Sano H. HPLC analysis of dental resin composites components. J Biomed Mat Res. 1999;47:374-8.

[133] Al-Hiyasat AS, Darmani H, Elbetieha AM. Leached components from dental composites and their effects on fertility of female mice. Eur J Oral Sci. 2004;112:267-72.

[134] Rudel RA, Melly SJ, Geno PW, Sun G, Brody JG. Identification of alkylphenols and other estrogenic phenolic compounds in wastewater, septage, and groundwater on Cape Cod, Massachusetts. Environ Sci Technol. 1998;32:861-9.

[135] Matsumoto H, Adachi S, Suzuki Y. Bisphenol A in ambient air particulates responsible for the proliferation of MCF-7 human breast caner cells and its concentration changes over 6 months. Arch Environ Con Tox. 2005;48 (4):459-66.

[136] Yoo SD, Shin BS, Lee BM et al. Bioavailability and mammary excretion of bisphenol a in Sprague-Dawley rats. J Toxicol Environ Health A. 2001;64:417-26.

[137] Negishi T, Tominaga T, Ishii Y et al. Comparative study on toxicokinetics of bisphenol A in F344 rats, monkeys (Macaca fascicularis), and chimpanzees (Pan troglodytes). Exp Anim. 2004;53:391-4.

[138] Moors S, Diel P, Degen GH. Toxicokinetics of bisphenol A in pregnant DA/Han rats after single i.v. application. Arch Toxicol. 2006;80:647-55.

[139] Savabieasfahani M, Kannan K, Astapova O, Evans NP, Padmanabhan V. Developmental programming: differential effects of prenatal exposure to bisphenol-A or methoxychlor on reproductive function. Endocrinology. 2006;147:5956-66.

[140] Xiao Q, Li Y, Ouyang H, Xu P, Wu D. High-performance liquid chromatographic analysis of bisphenol A and 4-nonylphenol in serum, liver and testis tissues after oral administration to rats and its application to toxicokinetic study. J Chromatogr B Analyt Technol Biomed Life Sci. 2006;830:322-9.

Table 1: BPA levels in human serum & tissues

Authors	Year	Detection method	Sensitivity (ng/ml)	Endpoint(s)	Levels found [ng/ml (ppb), mean ± SEM]	Unit if not ng/ml	nM equivalence	Other chemicals examined
Sajiki et al [15]	1999	Electrochemical detection	0.2	Healthy human serum	0 - 1.6		0 - 7.0	
		MS/ESI	0.1					
Fung et al. [67]	2000	HPLC/FD	5	Blood collected before and after dental sealant application	not detected			
Inoue et al [18]	2000	HPLC with electrochemical detection	0.01 in solvent	Healthy human serum	0.32		1.4	
		Coulometric array	0.05 in serum					
Inoue et al [113]	2001	LC-MS	0.1	Human plasma or serum	ND - 1.0		ND - 4.4	BADGE
Ikezuki et al [19]	2002	ELISA	0.3 in serum	Female nonpregnant 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 wk)	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 [20]	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 & Tsutsumi [23]	2002	ELISA	0.3 in serum	Normal male serum	1.49 ± 0.11		6.5 ± 0.48	Total & 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 & Mori [114]	2002	GC-MS	?	Umbilical cords at birth	Mean, 4.4 ± 1.5; range, 0.11 - 15.2	ng/g tissue		
Yamada et al [21]	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 [115]	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. [116]	2003	SPE GC-MS	0.09	Breast milk	range: 0.65 - 0.70	ng/g milk		Nonylphenol
Tan & Mohd [22]	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 [117]	2004	ELISA	0.5 (from Kodaira et al)	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 [27]	2004	DIB-Cl derivatization/ HPLC	0.11	Breast milk	0.61 ± 0.042		2.7 ± 0.18	
Takeuchi et al [24]	2004	ELISA	0.3 in serum	Serum- nonobese normal	0.71 ± 0.09		3.1 ± 0.39	Total & free T, DHEAS, androstenedione
				Serum- Nonobese 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 [42]	2005	ELISA	0.5 (from Kodaira et al)	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. [103]	2005	LC-MS/MS	1.14	Healthy human plasma	not detected			
Engel et al [26]	2006	HPLC/ electrochemical detection	0.5	residual amniotic fluid from amniocentesis, <20 wk gestation	0.55 (10% > 0.5 ng/ml)		2.41	enterolactone, daidzein & genistein
Joskow et al. [70]	2006	GC-MS (+ glucuronidate 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 hour after Delton sealant application	7.86 ± 4.24		34.5 ± 18.6	

				Saliva immediately after Helioseal sealant application Saliva 1 hour after Helioseal sealant application	0.54 ± 0.20 0.21 ± 0.013		2.4 ± 0.88 0.92 ± 0.06	
Ye et al. [28]	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. [29]	2007	ELISA	0.3	Human colostrum	3.41 ± 0.013		15.0 ± 0.06	

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 ± SEM]				Unit if not ng/ml	Estimated Daily Intake	Other chemicals examined
							Uncon BPA	BPA-gluc	BPA-sulfate	Total BPA			
Brock et al. [118]	2001	GC-MS	0.12	5 specimen pools from at least 5 people	glucuronidase	5/5 pools	below level of detection			range 0.11 - 0.51			
Ouchi & Watanabe [34]	2002	HPLC-ECD with column switching	0.2	Morning samples from 48 women students	glucuronidase	1/48 (free BPA); 100% BPA-Glu	range ND - 0.2	range 0.2-19.1				0.6 - 71.4 µg/day	
Kim et al. [33]	2003	RP-HPLC/FD	0.28	15 Male Korean volunteers 15 Female Korean volunteers	glucuronidase & sulfatase		0.58 ± 0.14 0.56 ± 0.10	2.34 ± 0.85 1.00 ± 0.34	0.49 ± 0.27 1.20 ± 0.32	2.82 ± 0.73 2.76 ± 0.54			
Matsumoto et al. [35]	2003	HPLC	1.7	50 University students in 1992 56 University students in 1999	glucuronidase & sulfatase	82% detection 61% detection						10 µg/g creatine	
Tsukioka et al. [119]	2003	NCI-GC/MS	0.1	6 urine samples	glucuronidase	100% detection				Range 0.2 – 3.8, mean 1.6			
Yang et al. [104]	2003	HPLC/FD	0.012	73 Koreans with various SULT1A1 polymorphisms	glucuronidase	75% detection				range 0.68-586.14, mean ~ 9.5			
Calafat et al. [31]	2005	GC-MS	0.1	reference population- 184 American males reference population- 210 American females	glucuronidase	96% detection 94% detection				1.63 1.12	µg/L (µg/g creatinine) µg/L (µg/g creatinine)		4-nonylphenol
Liu et al. [120]	2005	HPLC with ECD	0.5	9 girls 24 adults	glucuronidase	89% detection 52% detection				range 0.04 - 16.6, median 2.4 range ND - 2.24, median			daidzein, genistein & enterolactone

										0.47			
Volkel et al. [103]	2005	HPLC-MS/MS	1.14	6 subjects orally administered 25ug BPA	glucuronidase	2/6 samples	below LOD	below LOQ					
Ye et al. [121]	2005	online SPE-HPLC-MS/MS	0.3	30 demographically diverse volunteers	glucuronidase & 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. [70]	2006	GC-MS	0.1	Urine prior to dental sealant application- 14 men Urine immediately after Delton sealant application Urine 1 hour after Delton sealant application Urine immediately after Helioseal sealant application Urine 1 hour after Helioseal sealant application	glucuronidase glucuronidase glucuronidase glucuronidase glucuronidase					2.41 ± 0.33 27.3 ± 13.03 7.34 ± 1.44 7.26 ± 6.04 2.06 ± 0.47			
Yang et al. [43]	2006	HPLC/FD	0.026	172 Koreans with various SULT1A1 polymorphisms	glucuronidase	97.5% detection				range 0.03-62.4, median 7.86			
Wolff et al. [32]	2007	HPLC-MS/MS	0.36	90 young girls, aged 6-9	glucuronidase	94% detection				range ND – 54.3, mean 2.0			Phytoestrogens pthalates, & 8 other phenols

Table 3: Summary of epidemiology studies

Authors	Year	Study Type	Measurement of BPA	Health related outcome	Relationship between BPA & disease	Limitations
Hanaoka et al [41]	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 & Tsutsumi [23]	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 [21]	2002	Case control: 48 cases with abnormal karyotype, 200 controls (20 per year) selected from women carrying fetuses with normal karyotypes	BPA levels in materal serum & 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 [115]	2003	Cross-sectional: 9 healthy pregnant women, 21 women with sterility	BPA levels in serum & cord blood from pregnant women; serum & 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 [39]	2003	Observational: 9 pre-school aged children monitored for 48 hours	Urinary BPA levels, BPA levels in environmental samples		Primary route of BPA exposure was dietary.	Small sample size
Hiroi et al [117]	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 [24]	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 & 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 [42]	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 [40]	2006	Observational: 257 preschool children	Urinary BPA levels, BPA levels in environmental samples		Primary route of BPA exposure was dietary	
Yang et al [43]	2006	Cross-sectional: 68 adults appearing for regular check-up	Urinary BPA (HPLC)	Sister chromatid exchange in peripheral lymphocytes (untreated and MNNG-treated at .2mM, .4mM or .6mM); self-reported reproductive history and symptoms	Urinary BPA positively associated with SCE in untreated and MNNG-treated at .2mM. No association with SCE for MNNG-treated at higher doses. No association between BPA and self-reported reproductive history or symptoms.	

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. [122]	1997	24 polycarbonate baby bottles	HPLC/FD	0.03 ug/g		infant feed in contact with baby bottles after simulated use		not detected in any sample, before or after simulated use	
Sun et al. [49]	2000	2 polycarbonate baby bottles	HPLC with chemiluminescence detection	0.38 ng/ml		water in contact with new bottles for 30 min at 95C 2nd test of water in contact with bottles for 30 min at 95C water in contact with bottles for 30 min at 95C after brushing		Bottle A: 0.59 ± 0.04; Bottle B: 0.75 ± 0.045 Bottle A: 0.13 ± 0.005; Bottle B: 0.16 ± 0.01 Bottle A: 0.18 ± 0.01; Bottle B: trace levels	
D'Antuono et al. [123]	2001	4 brands of polycarbonate baby bottles purchased in Argentina	LC-ED	0.2 ng/ml		distilled water in contact with baby bottle for 30 sec at 100C		1.2	
Brede et al. [50]	2003	12 polycarbonate baby bottles purchased in Norway subjected to simulated use	SPE-GC (verified by MS)	0.1 ng/ml		water food simulant in contact with new bottles for 1hr at 100C food simulant in contact with bottles for 1hr at 100C after 51 washes & 13 brushes food simulant in contact with bottles for 1hr at 100C after 169 washes & 23 brushes		0.23 ± 0.03 8.4 ± 1.2 6.7 ± 1.2	
Wong et al. [48]	2005	28 polycarbonate baby bottles purchased in Singapore	HPLC (verified by GC-MS)	3 ug/g 50 ng/square inch		composition of plastic material from baby bottles 10% ethanol in contact with bottles for 8 hr at 70C corn oil in contact with bottles for 8 hr at 100C	detected in 19 of 28 samples, mean: 28.1	ND - 580 ND - 2560	ng/square inch ng/square inch

Consumer Plastics and Papers

Vinggaard et al. [53]	2000	9 paper towels from recycled paper 11 paper towels from virgin paper	GC/FTIR/MS	0.2mg/kg paper		paper towel composition paper towel composition	Range 0.55 - 24.1 Range ND - 0.12		
Nerin et al. [51]	2003	Plastic commercial containers for microwave	HPLC/FD (verified by GC-MS)	0.04 ug/g	0.1 ug/g	polycarbonate composition	30		ug/g
Sajiki et al. [124]	2003	polycarbonate plastic tubing	LC-MS	0.1 ng/ml		leaching to seawater at 20C per day leaching to seawater at 37C per day leaching to river water at 20C per day leaching to river water at 37C per day leaching to control water at 20C per day leaching to control water at 37C per day		1.6 11 0.2 4.8 0.15 0.8	
Lopez-Cervantes et al. [52]	2003	5 commercially available polyvinyl chloride plastic wraps	HPLC/FD (verified by GC-MS)			plastic wrap composition leaching into water after 10 days of exposure at 40C leaching into 3% acetic acid after 10 days of exposure at 40C leaching into olive oil after 10 days of exposure at 40C	Range ND - 483	 Range ND - 11.5 Range ND - 11.9 Range ND - 30.7	ug/g ug/square decimeter ug/square decimeter ug/square decimeter
Ozaki et al. [54]	2004	16 virgin paper products in food contact 12 recycled paper products in food contact	GC-MS	0.02 mg/kg paper		paper composition paper composition	Range ND - 0.36, detected in 81.3% of samples Range ND - 26, detected in 66.7% of samples		
Sajiki et al. [125]	2004	polycarbonate plastic tubing	HPLC			leaching (per day) to water over several weeks leaching (per day) to albumin (50 mg/ml)		0.5 3	

Lopez-Espinosa et al. [55]	2007	32 cardboard samples for take-out food 8 paper products for take-out food	HPLC (verified by GC-MS)	22.8 ng/ml		cardboard composition paper composition	Range ND - 18.17, detected in 46.9% of samples Range ND - 1.88, detected in 37.5% of samples		

Table 4B: Leaching levels from cans & 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. [56]	1995	Cans containing 20 different types of food product	HPLC (verified by MS)			Water autoclaved in cans for 30 min at 125C	Range 4 - 23	ug/can
Bae et al. [126]	2002	3 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. [127]	2002	Cans with epoxy resin linings	HPLC/FD			Water sealed into cans, heated for 30 min at 121C	Range 7 - 31	
Takao et al. [58]	2002	Cans with epoxy resin linings	GC-MS	0.05		Water sealed into cans, unheated Water sealed into cans, heated for 30 min at 80C Water sealed into cans, heated for 30 min at 100C	detected in 100% of samples 1.6 - 16.7x higher than levels in unheated cans 1.7 - 55.4x higher than levels in unheated cans	
Kang et al. [57]	2003	Cans with epoxy resin linings	HPLC	1		Water autoclaved in cans for 30 min at 105C or 121C Glucose solution autoclaved in cans for 30 min at 121C Sodium chloride solution autoclaved in cans for 30 min at 121C Vegetable oil autoclaved in cans for 30 min at 121C	At 105C: 1.0; At 121C: 5.0 Range 7-8 >10 Range 16-18	

Table 4C: Leachates detected in food products

Authors	Year	Sample	Detection method	Sensitivity	Quantification limit	Endpoint(s)	Leaching levels (ng/g)	Units if not ng/g
Brotons et al. [56]	1995	canned vegetables and fatty foods	HPLC (verified by MS)			liquid phase of vegetables packed in lacquer-coated cans	Range ND - 22.9	ug/can
Biles et al. [128]	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 & Borodinsky [129]	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. [60]	2001	canned vegetables & fruit	HPLC/UV	5 ng/g		solid portion of canned food aqueous portion of canned food	Range <10.0 - 95.3 not detected i	
Goodson et al. [61]	2002	survey of canned foods	GC-MS	2 ng/g	7 ng/g	canned vegetables, infant formula, fish, beverages, soup, meat	detected in 38 of 62 samples	
Kang & Kondo [127]	2002	canned instant coffee	HPLC/FD	10 ng/ml 2 ng/ml		decaffeinated instant coffee non-decaffeinated instant coffee caffeine solution (0.1mg/mL) caffeine solution (1.0mg/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. [59]	2002	canned pet foods	HPLC/FD			canned cat food canned dog food	Range 13 - 136 Range 11 - 206	
Munguia-Lopez et al. [130]	2002	cans containing jalapenos & acidic food stimulants	HPLC/FD (verified by GC-MS)	2 ng/ml		canned jalapeno peppers acid food stimulant stored in cans for 4hrs at room temperature (25C) acid food stimulant stored in cans for 4hrs at 35C acid food stimulant stored in cans for 160 days at 25C acid food stimulant stored in cans for 160 days at 35C	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. [107]	2003	levels in honey	LC-MS	20 ng/ml		107 honey samples	Range ND - 33.3	
Kuo et al. [64]	2004	powdered milk & infant formula	GC-MS		1 ng/g	milk & infant formula	Range 45 - 113	
Munguia-Lopez et al. [62]	2005	cans containing tuna fish or fatty-food stimulant	HPLC (verified by GC-MS)	5 ng/ml		canned tuna fish	Range <7.1 - 102.7	

						fatty-food stimulant stored in cans for 4hrs at room temperature (25C) fatty-food stimulant stored in cans for 4hrs at 35C fatty-food stimulant stored in cans for 160 days at 25C fatty-food stimulant stored in cans for 160 days at 35C	not detected in any sample 646.5 ± 63.4 186.1 ± 18.6 398.7 ± 30.9	
Maragou et al. [131]	2006	canned milk (whole evaporated, partly skimmed evaporated, powdered infant formula)	SPE with LC-ESI-MS	1.7 ng/g	5.1 ng/g	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 (ug/ml)	Leaching levels (ug/ml)	Units if not ug/ml
Olea et al. [65]	1996	4 commercial composite dental resins 18 patients with 50mg of sealant applied to a total of 12 molars	HPLC (verified by GC-MS)			resin composition saliva 1hr after application	At neutral pH, range 0.005 - 0.677	Range 3.3 - 30	ug/mg sealant
Nathanson et al. [74]	1997	7 commercial dental sealants	HPLC (verified by GC-MS)	0.1ng/mg		Eluates from sealants treated with light in vitro	undetected in any sample		
Arenholt-Bindslev et al. [66]	1999	8 patients with a total of 38 mg of sealant applied to a total of 4 molars	HPLC	100	300	saliva immediately after application saliva 1hr after application saliva 24h after application		Range ND - 2.8, mean 1.43 undetected in any sample undetected in any sample	
Lewis et al. [71]	1999	28 commercial composite dental resins	HPLC with infrared analysis			resin composition	detected in 2 products		
Noda et al. [132]	1999	5 dental resin composites	HPLC (verified by UV spectra)			raw resin composition	0.001 - 0.0022		ug/mg sealant
Schmalz et al. [72]	1999	5 commercial dental resins	HPLC	200		Eluates from sealants made from BADGE Eluates from sealants made from Bis-GMA Eluates from sealants made from Bis-DMA	Range 2 - 8 not detected Range 4 - 155		
Fung et al. [67]	2000	22 patients with 32mg of sealants applied to a total of 4 molars	HPLC/FD	5		saliva 1-3hr after application		Range 0.0058-0.1056	
Pulgar et al. [73]	2000	8 dental compounds	HPLC (verified by GC-MS)	200	230	composition before in vitro polymerization composition after in vitro polymerization	At neutral pH, range ND - 155 At neutral pH, range ND - 42.8		
Tarumi et al. [75]	2000	16 commercial dental resins	HPLC (verified by GC-MS)	0.1		Resin composition	undetected in any sample		

Zafra et al. [68]	2002	8 patients undergoing dental repairs	GC-MS	3	12	saliva 1hr after application		Range 0.0153 - 0.0324	
Al-Hiyasat et al. [133]	2004	Resin based Z-100 dental sealant	HPLC			Eluates from sealant samples after 3 weeks in vitro	78		
Wada et al. [76]	2004	24 commercial dental composites	GC-MS	1		eluates from composites	undetected in any sample		
Sasaki et al. [69]	2005	21 patients treated with one of 9 resins	ELISA			saliva immediately after application saliva after application and gargling		Range 0.0210 - 0.0601 Range 0.0016 - 0.0047	
Joskow et al. [70]	2006	Patients treated with one of two dental sealants	GC-MS	0.1		Saliva prior to dental sealant application Saliva immediately after Delton sealant application Saliva 1 hour after Delton sealant application Saliva immediately after Helioseal sealant application Saliva 1 hour after Helioseal sealant application		0.00030 ± 0.000043 0.0428 ± 0.01022 0.00786 ± 0.00424 0.00054 ± 0.00020 0.00021 ± 0.000013	

Table 5: Environmental levels of BPA in air, dust & 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. [134]	1998	waste water, septage and ground water	HPLC GC/MS	0.0054 ug/l	0.0162 ug/l	Untreated septage Untreated wastewater Treated septage & wastewater	detected at 4 of 5 sites detected at 3 of 4 sites 100% detection (3 sites)	Range 110-1700 Range 94-150 Range 20-55	
Kuch & Ballschmiter [82]	2001	water	SPE HRGC-(NCI)-MS	0.04 ng/l		sewage treatment works effluents river water in Germany drinking water	detected at 15 of 16 sites 100% detection (31 sites) 100% detection (10 sites)	Range: 4.8 - 47; mean 16 Range: 0.5 - 14; mean 4.7 Range: 0.5 - 2.0; mean 1.1	
Rudel et al. [87]	2001	residential air & dust	GC-MS			indoor air dust samples	Detected in 3 of 7 homes/offices and one plastics workplace Detected in 3 of 6 homes/offices	Range 2-3 in homes/offices and 208 in plastics workplace Range 0.25-0.48	ng/cubic meter ug/g
Yamamoto et al. [80]	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. [83]	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 - 21000	
Kolpin et al. [84]	2002	surface water	SPE LC/MS-ESI		90 ng/l	US streams and wastewater	41.2% detection	median: 140	
Zafra et al. [68]	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. [79]	2003	landfill leachates	GC-MS			raw landfill leachates treated landfill leachates		3.61 46200	mg/l
Kawagoshi et al. [78]	2003	landfill leachates	GC-MS	500 ng/l		groundwater outside Japanese landfill		740000	
Rudel et al. [86]	2003	indoor air & dust	GC-MS			indoor air house dust samples	Not detected in 120 homes Detected in 86% of 118 homes	<18 Range: 0.2-17.6; median 0.821	ng/cubic meter ug/g

Matsumoto et al. [135]	2005	air particulates	GC-MS	0.01 ng/cubic meter		urban ambient outdoor air		Range: 0.02 - 1.92; mean 0.51	ng/cubic meter

Table 6: Summary of acute metabolic studies

Authors	Year	Species	Dose adminis-tered	Dosing method	Detection method	Sensitivity	Endpoint(s)	Levels found (% of dose administered)				Levels measured (ug/g)			*Unconj BPA (ng/ml) scaled to oral dose of 50 ug/kg*
								Unconj BPA	BPA-gluc	BPA-sulfate	Total BPA	BPA Conj &/or Total	Unconj BPA	Units if not ug/g	
Miyakoda et al., 1999	1999	rats (female, GD 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 (female, GD 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)	10 mg/kg	oral			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. [88]	2000	rats (males)	10 mg/kg	oral	HPLC w/ GC-MS		urine collections for 72 hours	1.8	9.6	0.48					

							fecal collections for 72 hours	81.29								
		rats (female)	10 mg/kg	oral			urine collections for 72 hours	1.5	20.2	0.74						
							fecal collections for 72 hours	71.65								
		rats (males)	10 mg/kg	i.p.			urine collections for 72 hours	0.72	8.6	0.49						
							fecal collections for 72 hours	83.17								
		rats (female)	10 mg/kg	i.p.			urine collections for 72 hours	0.9	18.3	0.76						
							fecal collections for 72 hours	64.07								
		rats (males)	10 mg/kg	subcut			urine collections for 72 hours	0.77	9.2	0.59						
							fecal collections for 72 hours	80.19								
		rats (female)	10 mg/kg	subcut			urine collections for 72 hours	0.93	23.2	1.8						
							fecal collections for 72 hours	54.4								
		rats (male)	100 mg/kg	oral		100 ng/g	Blood, 0.083 h after dosing						*0.22*		0.11	
							Blood, 0.25 h after dosing						*0.17*		0.085	
							Blood, 0.5 h after dosing						*0.16*		0.08	
				i.p.		100 ng/g	Blood, 0.5 h after dosing						*8.3*			
							Blood, 2 h after dosing						*2*			
							Blood, 8 h after dosing						*0.56*			
				subcut		100 ng/g	Blood, 0.5 h after dosing						*5.1*			
							Blood, 2 h after dosing						*3.5*			
							Blood, 18 h after dosing						*0.2*			
		rats (female)	100 mg/kg	oral		100 ng/g	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.		100 ng/g	Blood, 0.5 h after dosing						*11*			
							Blood, 2 h after dosing						*1.9*			

							Blood, 24 h after dosing						*0.29*		
				subcut		100 ng/g	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.		10 ng/g	Blood, 0.5 h after dosing						*0.7*		
							Blood, 2 h after dosing						*0.18*		
							Blood, 4 h after dosing						*0.049*		
				subcut		10 ng/g	Blood, 0.5 h after dosing						*0.3*		
							Blood, 2 h after dosing						*0.33*		
							Blood, 12 h after dosing						*0.038*		
		rats (female)	10 mg/kg	oral		10 ng/g	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.		10 ng/g	Blood, 0.5 h after dosing						*0.85*		
							Blood, 2 h after dosing						*0.12*		
							Blood, 18 h after dosing						*0.018*		
				subcut		10 ng/g	Blood, 0.5 h after dosing						*0.28*		
							Blood, 2 h after dosing						*0.25*		
							Blood, 24 h after dosing						*0.016*		
Takahashi & Oishi [109]	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 hrs after treatment						0.29		0.0145
							maternal blood 24 hrs after treatment						*0.13*		0.0065
							maternal blood 48 hrs after treatment						*0.083*		0.00415
							maternal liver 20 min after dosing						171		
							maternal liver 6 hrs after treatment						8.55		
							maternal kidney 20 min after dosing						36.2		
							maternal kidney 6 hrs after treatment						1.81		
							fetuses 10 min after dosing						2		
							fetuses 20 min after dosing						9.22		
							fetuses 6 hrs after treatment						0.46		
Upmeier et al [99]	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	oral			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. [136]	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 ug/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. [94]	2002	monkey (male)	100 ug/kg	oral	HPLC w/ radioactivity, C-14-labeled BPA	3 ng/ml	fecal collections for 168 hours				2.14			
					S.A. 2.62 GBq/mmol (0.071 Ci/mmol)		urine collections for 168 hours				59.68			
							plasma, 0.5 hr after injection					0.098	</= 1.5%	ug/ml
							plasma, 2 hrs after injection					0.028	</= 1.5%	ug/ml
		monkey (female)	100 ug/kg	oral			fecal collections for 168 hours				3.08			
							urine collections for 168 hours				37.21			
							plasma, 0.5 hr after injection					0.095	</= 1.5%	ug/ml
							plasma, 2 hrs after injection					0.025	</= 1.5%	ug/ml
		monkey (male)	100 ug/kg	i.v.			fecal collections for 168 hours				1.84			
							urine collections for 168 hours				63.2			
							plasma, 0.5 hr after injection					0.141		ug/ml
							plasma, 2 hrs after injection					0.032		ug/ml
		monkey (female)	100 ug/kg	i.v.			fecal collections for 168 hours				1.95			
							urine collections for 168				50.37			

							hours								
							plasma, 0.5 hr after injection					0.161		ug/ml	
							plasma, 2 hrs after injection					0.036		ug/ml	
Uchida et al. [110]	2002	monkey (pregnant, gestational day 150)	50 mg/kg	subcut	GC-MS	?	maternal serum 1 hr after treatment					6.1			
							fetal serum 1 hr after treatment					1.7			
							fetal liver 1 hr after treatment					65			
							fetal kidney 1 hr after treatment					37.5			
Volkel et al. [102]	2002	human	5 mg per person	oral	LC-MS/MS	1.37 ng/ml (6 nM)	urine						no free BPA present		
			(around 77 ug/kg bw)			2.28 ng/ml (10 nM)	blood						no free BPA present		
Domoradzki et al [97]	2003	rats (female)	10 mg/kg	oral	HPLC w/ radioactivity, C-14-labeled BPA	8-39 ng/g	plasma, 15 min after dosing					0.716	ND		
					S.A. 56 mCi/mmol (0.056 Ci/mmol)		plasma, 6 hrs after dosing					0.077	ND		
							fecal collections for 96 hours				77.82				
					S.A. 200 mCi/mmol (0.20 Ci/mmol)		urine collections for 96 hours				14.8				
		rats (pregnant, gestational day 6)					plasma, 15 min after dosing					0.37	ND		
							plasma, 6 hrs after dosing					0.175	ND		
							fecal collections for 96 hours				64.86				
							urine collections for 96 hours				21.96				
							embryos collected on GD 10				0				
		rats (pregnant, gestational day 17)					plasma, 15 min after dosing					1.028			
							plasma, 6 hrs after dosing					0.194			

							pooled plasma (to 12 h)						0.011-0.022		0.055 - 0.110
							fecal collections for 96 hours				72.03				
							urine collections for 96 hours				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. [95]	2003	rats (males)	100 mg/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 hours	1.1	6.5	0.3					
							fecal collections for 72 hours	61	ND	ND					
							bilary excretions within 18 hours		41						
			100 ug/kg	oral			urine collections for 24 hours				6.3				
							urine collections for 48 hours				10.1				
							fecal collections for 48 hours				81.6				
			100 ug/kg	i.v.			urine collections for 24 hours				8.4				
							urine collections for 48 hours				12.5				
							fecal collections for 48 hours				77.6				
			100 ug/kg	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. [17]	2003	mice (pregnant, GD17)	25 ug/kg	subcut	HPLC w/ radioactivity, tritium-labelled BPA	?	urine collections for 24 hours				5.72				
					S.A. 572.2 kBq/µg (3.53 Ci/mmol)		fecal collections for 24 hours				21.2				
							maternal blood 24 h after treatment					2.2		ng/ml	
					S.A. 811.3 kBq/µg (5.0 Ci/mmol)		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	
		pregnant, GD17	25 ug/kg	subcut			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	
		nonpregnant females	25 ug/kg	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	
							maternal liver 24 h after treatment					0.0061	ND	ng/g	
		pregnant, GD17	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. [100]	2004	rats (neonatal days 4, 7 and 21, and adult 11 weeks)	1 mg/kg	oral	HPLC w/ radioactivity, C-14-labeled BPA	6-10 ng/g	blood levels in PND4 rats 6hrs after treatment					female: 0.37; male: 0.38	female: 0.01; male: 0.008		
					S.A. 56 mCi/mmol		blood levels in PND7 rats 6hrs after treatment					female: 0.35; male: 0.32			
					(0.056 Ci/mmol)		blood levels in PND21 rats 6hrs after treatment					female: 0.33; male: 0.39			
			10 mg/kg	oral	S.A. 200 mCi/mmol	14-48 ng/g	blood levels in PND4 rats 6hrs after treatment					female: 3.55; male: 5.56			
					(0.20 Ci/mmol)		blood levels in PND7 rats 6hrs after treatment					female: 3.57; male: 3.37			

							blood levels in PND21 rats 6hrs after treatment						female: 3.52; male: 3.18				
							Plasma:										
			1 mg/g	oral		6-10 ng/g	PND 4 females, 0.25 hrs after dosing								*0.056*		
							PND 4 females, 1.5 hrs after dosing								*0.021*		
							PND 4 females, 18 hrs after dosing								*0.017*		
							PND 4 males, 0.25 hrs after dosing								*0.031*		
							PND 4 males, 1.5 hrs after dosing								*0.0064*		
							PND 4 males, 12 hrs after dosing								*0.026*		
			1 mg/g	oral		6-10 ng/g	PND 7 females, 0.25 hrs after dosing								*0.21*		
							PND 7 females, 1.5 hrs after dosing								*0.023*		
							PND 7 females, 3 hrs after dosing								*0.021*		
							PND 7 males, 0.25 hrs after dosing								*0.043*		
							PND 7 males, 1.5 hrs after dosing								*0.012*		
							PND 7 males, 3 hrs after dosing								*0.03*		
			1 mg/g	oral		6-10 ng/g	PND 21 females, 3 hrs after dosing								*0.0067*		
							PND 21 males, 0.25 hrs after dosing								*0.0076*		
							PND 21 males, 3 hrs after dosing								*0.0045*		
			1 mg/g	oral		6-10 ng/g	11 wk females								*NQ*		
							11 wk males								*NQ*		

			10 mg/g	oral		14-48 ng/g	PND 4 females, 0.25 hrs after dosing						*10.2*		
							PND 4 females, 0.75 hrs after dosing						*4.1*		
							PND 4 females, 1.5 hrs after dosing						*0.185*		
							PND 4 females, 6 hrs after dosing						*0.097*		
							PND 4 males, 0.25 hrs after dosing						*49*		
							PND 4 males, 0.75 hrs after dosing						*1.1*		
							PND 4 males, 1.5 hrs after dosing						*2.2*		
							PND 4 males, 18 hrs after dosing						*0.091*		
			10 mg/g	oral		14-48 ng/g	PND 7 females, 0.25 hrs after dosing						*5.9*		
							PND 7 females, 1.5 hrs after dosing						*0.44*		
							PND 7 females, 12 hrs after dosing						*0.094*		
							PND 7 males, 0.25 hrs after dosing						*1.15*		
							PND 7 males, 1.5 hrs after dosing						*0.2*		
							PND 7 males, 18 hrs after dosing						*0.053*		
			10 mg/g	oral		14-48 ng/g	PND 21 females, 0.25 hrs after dosing						*0.1*		
							PND 21 females, 1.5 hrs after dosing						*0.2*		
							PND 21 females, 6 hrs after dosing						*0.11*		
							PND 21 males, 0.25 hrs after dosing						*0.057*		
							PND 21 males, 1.5 hrs after dosing						*0.15*		
							PND 21 males, 12 hrs after dosing						*0.026*		

			10 mg/g	oral		14-48 ng/g	11 wk females, 0.75 hrs after dosing						*0.063*		0.315
							11 wk males, 0.25 hrs after dosing						*0.024*		0.12
							11 wk males, 0.75 hrs after dosing						*0.012*		0.06
							11 wk males, 1.5 hrs after dosing						*0.011*		0.055
Negishi et al. [137]	2004	rats (female)	10 mg/kg	oral	BPA ELISA	12.5 ng/ml	serum 0.5 h						*NQ*	ug/ml	
							serum 2 h						0.011	ug/ml	0.055
							serum 24 h						*NQ*	ug/ml	
		chimpanzee 1 (female)	10 mg/kg	oral			serum 0.5 h						*0.32*	ug/ml	
							serum 2 h						*0.14*	ug/ml	
							serum 8 h						*0.051*	ug/ml	
		chimpanzee 2 (female)					serum 0.5 h						*0.093*	ug/ml	
							serum 2 h						*0.079*	ug/ml	
							serum 8 h						*0.045*	ug/ml	
		cynomolgus monkeys (female)	10 mg/kg	oral			serum 0.5 h						*2.8*	ug/ml	
							serum 2 h						*0.35*	ug/ml	
							serum 6 h						*0.048*	ug/ml	
		rats (female)	100 mg/kg	oral			serum 0.5 h						*0.58*	ug/ml	0.29
							serum 2 h						*0.090*	ug/ml	0.045
							serum 24 h						*0.020*	ug/ml	0.01
		cynomolgus monkeys (female)	100 mg/kg	oral			serum 0.5 h						*5.4*	ug/ml	
							serum 2 h						*4.1*	ug/ml	
							serum 24 h						*0.12*	ug/ml	
		rats (female)	10 mg/kg	subcut			serum 0.5 h						*0.49*	ug/ml	
							serum 2 h						*0.53*	ug/ml	
							serum 6 h						*0.13*	ug/ml	
		chimpanzee 1 (female)	10 mg/kg	subcut			serum 0.5 h						*0.86*	ug/ml	
							serum 2 h						*2.0*	ug/ml	
							serum 24 h						*0.052*	ug/ml	

		chimpanzee 2 (female)					serum 0.5 h					*0.68*	ug/ml		
							serum 2 h					*1.0*	ug/ml		
							serum 24 h					*0.053*	ug/ml		
		cynomolgus monkeys (female)	10 mg/kg	subcut			serum 0.5 h					*0.64*	ug/ml		
							serum 2 h					*5.9*	ug/ml		
							serum 24 h					*0.034*	ug/ml		
		rats (female)	100 mg/kg	subcut			serum 0.5 h					*2.9*	ug/ml		
							serum 2 h					*2.75*	ug/ml		
							serum 24 h					*0.35*	ug/ml		
		cynomolgus monkeys (female)	100 mg/kg	subcut			serum 0.5 h					*6.0*	ug/ml		
							serum 2 h					*16*	ug/ml		
							serum 24 h					*2.9*	ug/ml		
Kurebayashi et al. [93]	2005	rats (males)	500 ug/kg	oral	Radioluminography of C-14-BPA-derived	2 dpm/20 ul (<0.5 ng/ml)	plasma 0.25 h					*34*	2.30%		
					radioactivity								*=> 0.78*	ng/ml	0.078
					S.A. 2.62 GBq/mmol		plasma 0.5 h					*28*		ng/ml	
					(0.071 Ci/mmol)		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%		
													######	ng/ml	0.0028
			100 ug/kg	oral			plasma 0.5 h					*7.1*		ng/ml	
							plasma 2 h					*3.6*		ng/ml	
							plasma 24 h					*2.7*		ng/ml	
			20 ug/kg	oral			plasma 0.5 h					*1.5*		ng/ml	
							plasma 2 h					*1.4*		ng/ml	
							plasma 24 h					*0.51*		ng/ml	
			500 ug/kg	i.v.			plasma 0.5 h					*130*		ng/ml	
							plasma 2 h					*55*		ng/ml	
							plasma 24 h					*10*		ng/ml	

			100 ug/kg	i.v.			plasma 0.5 h					*29*	ng/ml	
							plasma 2 h					*14*	ng/ml	
							plasma 24 h					*4.2*	ng/ml	
		rats (females)	500 ug/kg	oral			plasma 0.5 h					*14*	ng/ml	
							plasma 2 h					*16.5*	ng/ml	
							plasma 24 h					*7.2*	ng/ml	
			100 ug/kg	oral			plasma 0.5 h					*4.7*	ng/ml	
							plasma 2 h					*3.6*	ng/ml	
							plasma 24 h					*1.5*	ng/ml	
			20 ug/kg	oral			plasma 0.5 h					*0.51*	ng/ml	
							plasma 2 h					*0.65*	ng/ml	
							plasma 24 h					*0.23*	ng/ml	
			500 ug/kg	i.v.			plasma 0.5 h					*160*	ng/ml	
							plasma 2 h					*47*	ng/ml	
							plasma 24 h					*14*	ng/ml	
			100 ug/kg	i.v.			plasma 0.5 h					*32*	ng/ml	
							plasma 2 h					*8.9*	ng/ml	
							plasma 24 h					*2.9*	ng/ml	
		rats, 12 d gestation	500 ug/kg	oral			blood 0.5 h					43.32	ng/ml	
							blood 24 h					4.33	ng/ml	
		rats, 15 d gestation	500 ug/kg	oral			blood 0.5 h					37.51	ng/ml	
							blood 24 h					3.83	ng/ml	
		rats, 18 d gestation	500 ug/kg	oral			blood 0.5 h					30.99	ng/ml	
							blood 24 h					10.79	ng/ml	
		rats (lactating females) (PND 11)	500 ug/kg	oral			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	

							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. [103]	2005	humans	25 ug per person (around 0.38 ug/kg bw)	oral	LC-MS/MS	1.14 ng/ml	urine levels in females within 5 hrs of treatment	ND - 2	75						
							urine levels in males within 5 hrs of treatment	ND - 2	85						
							plasma levels within 5 hrs of treatment	ND	detected						
Moors et al. [138]	2006	rats (pregnant d18)	10 mg/kg	i.v.	GC-MS after derivatization	15 ng/ml	maternal plasma, 5 min					3.8	2.9	ug/ml	
							maternal plasma, 2 h					0.7	0.3	ug/ml	
							maternal plasma, 6 h					0.8	0.1	ug/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. [139]	2006	sheep (pregnant Suffolk ewes), GD50	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	
		GD70		subcut, 40 days			maternal plasma, after 40 days of daily BPA treatment						*55*	ng/ml	
		GD90		subcut, 60 days			maternal plasma, after 60 days of daily BPA treatment						37.4	ng/ml	
Takeuchi et al. [25]	2006	rats (female)	50 mg/kg	subcut	ELISA	0.5 ng/ml	intact, serum 1h					*0.66*		ug/ml	
							intact, serum 2 h					0.7496		ug/ml	
							intact, serum 3 h					*0.64*		ug/ml	
			50 mg/kg	subcut			intact, serum, 2 h					*0.65*		ug/ml	
							ovx, serum, 2 h					*0.68*		ug/ml	
							ovx+TP 0.01, serum, 2 h					*0.79*		ug/ml	
							ovx+TP 0.1, serum, 2 h					*0.98*		ug/ml	
							ovx+TP 1.0, serum, 2 h					*1.4*		ug/ml	
			0 mg/kg (basal)				intact, serum, 0 h (basal)					0.00438		ug/ml	
							ovx, serum, 0 h (basal)					0.0041		ug/ml	
							ovx+TP 0.01, serum, 0 h (basal)					0.00451		ug/ml	
							ovx+TP 0.1, serum, 0 h (basal)					0.00534		ug/ml	
							ovx+TP 1.0, serum, 0 h (basal)					0.00576		ug/ml	
Tominaga et al [101]	2006	rats (female)	10 mg/kg	oral	LC–MS/MS w/ ESI	0.2 ng/ml	serum 0.5 h						*2.1*	ug/L =	0.0105
							serum 2 h						*0.63*	ng/ml	0.00315
							serum 24 h						*0.62*	ng/ml	0.0031
		chimpanzees (female)	10 mg/kg	oral			serum 0.5 h						*5.3*	ng/ml	
							serum 2 h						*2.9*	ng/ml	
							serum 24 h						*0.35*	ng/ml	

		cynomolgus monkeys (female)	10 mg/kg	oral			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	oral			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)	100 mg/kg	oral			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)	10 mg/kg	subcut			serum 0.5 h						*510*	ng/ml	
							serum 2 h						*580*	ng/ml	
							serum 24 h						*16.7*	ng/ml	
		cynomolgus monkeys (female)	10 mg/kg	subcut			serum 0.5 h						*640*	ng/ml	
							serum 2 h						*4100*	ng/ml	
							serum 24 h						*34*	ng/ml	
		rats (female)	100 mg/kg	subcut			serum 0.5 h						*2300*	ng/ml	
							serum 2 h						*2250*	ng/ml	
							serum 24 h						*9*	ng/ml	
		cynomolgus monkeys (female)	100 mg/kg	subcut			serum 0.5 h						*3400*	ng/ml	
							serum 2 h						*6950*	ng/ml	
							serum 24 h						*1500*	ng/ml	
		rats (female)	10 mg/kg	subcut	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)	10 mg/kg	subcut			serum 0.5 h					*975*		ng/ml	
							serum 2 h					*440*		ng/ml	
							serum 24 h					*8.8*		ng/ml	
		cynomolgus monkeys (female)	10 mg/kg	subcut			serum 0.5 h					*8800*		ng/ml	
							serum 2 h					*2000*		ng/ml	
							serum 24 h					*33*		ng/ml	
Xiao et al. [140]	2006	rats (male)	100 mg/kg	oral	HPLC w/ fluorescence detection	2.8 ng/ml	serum 1 h						*1.4*	ug/ml	0.7
							serum 2 h						*2.8*	ug/ml	1.4
							serum 24 h						*1.8*	ug/ml	0.9
							serum 48 h						*0.88*	ug/ml	0.44
							serum 72 h						*0.35*	ug/ml	0.175
			100 mg/kg	oral w/ NP			serum 1 h						*2.3*	ug/ml	1.15
							serum 2 h						*3.3*	ug/ml	1.65
							serum 24 h						*2.9*	ug/ml	1.45
							serum 48 h						*0.77*	ug/ml	0.385
							serum 72 h						*0.29*	ug/ml	0.145

a - Numbers in italics have been digitized from the published figures and are approximate

b - Scaling by approximation of linearity of circulating level of BPA with dose within dosing method (P, 2000; refs)

c - Current Reference Dose for BPA is 50 ug/kg bw/d; 45 publications from the In Vivo panel report describe effects after oral dose at and below this level

subcut - subcutaneous; i.p. - intraperitoneal; i.v. - intravenous

NQ - not quantifiable; ND - not detected; PND - Post Natal Day; NP - nonylphenol

Figure Legends

Figure 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.

Figure 2. Subsets of the data of Figure 1 grouped by dose (A-C) or by animal type (D-F). Subsets of the data from Figure 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 ug/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 4 data sets, 2 consisting of single time points. Panel E graphs circulating levels after oral dosing of adult, nonpregnant 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).

Table 6. Summary of acute metabolic studies. Results from 21 published studies on the pharmacokinetics / toxicokinetics of BPA are summarized below listing animal, dose and route of exposure, method of detection for BPA and BPA metabolites with sensitivity or limit of detection of the method. The levels measured in the listed matrix are given, with a separate column for unconjugated, biologically active BPA, where measured. Where data were presented only in figures, the data were obtained from the pdf form of the figures from the publication, and the data were recovered with the program GraphClick (v. 2.9.2, copyright Arizona Software, 2007); the recovered data should be considered approximate, and are shown in italics in the table. Rather than list all of the recovered data points, three points were selected at or close to 0.5 h, 2 h and 24 h after oral dosing, which were time points common to many of the studies, or the data at all of the time points if there were three or fewer. Seventeen of the studies contained data from oral dosing, and of these, 11 studies included data on unconjugated BPA in blood, plasma or serum after the oral dosing, and these data (circulating unconjugated BPA) are given in the last column of the table after scaling the level measured after various oral doses to a single dose of 50 μg/kg body weight, the reference dose for BPA (see text). 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.