Accepted Manuscript

Title: Bisphenol A and Human Health: A review of the literature

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PII: S0890-6238(13)00345-6
DOI: http://dx.doi.org/doi:10.1016/j.reprotox.2013.08.008
Reference: RTX 6876

To appear in: *Reproductive Toxicology*

Received date: 1-3-2013
Revised date: 13-6-2013
Accepted date: 21-8-2013

Please cite this article as: Rochester JR, Bisphenol A and Human Health: A review of the literature., *Reproductive Toxicology* (2013), http://dx.doi.org/10.1016/j.reprotox.2013.08.008

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Bisphenol A and Human Health: A review of the literature.

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Abstract

There is growing evidence that bisphenol A (BPA) may adversely affect humans. BPA is an endocrine disruptor that has been shown to be harmful in laboratory animal studies. Until recently, there were relatively few epidemiological studies examining the relationship between BPA and health effects in humans. However, in the last year, the number of these studies has more than doubled. A comprehensive literature search found 91 studies linking BPA to human health; 53 published within the last year. This review outlines this body of literature, showing associations between BPA exposure and adverse perinatal, childhood, and adult health outcomes,

including reproductive and developmental effects, metabolic disease, and other health effects. These studies encompass both prenatal and postnatal exposures, and include several study designs and population types. While it is difficult to make causal links with epidemiological studies, the growing human literature correlating environmental BPA exposure to adverse effects in humans, along with laboratory studies in many species including primates, provides increasing support that environmental BPA exposure can be harmful to humans, especially in regards to behavioral and other effects in children.

Key Words

Bisphenol A

Human

Endocrine Disrupting Chemicals

Epidemiology

Reproduction

Development

Metabolic Disease

Thyroid

Abbreviations and Definitions

8-OHdG: 8-hydoxydeoxyguanosine

AGD: anogenital distance

ANA: antinuclear antibodies

BADGE: bisphenol A diglycidyl ether

BASC-2: Behavioral Assessment System for Children

bisGMA: bisphenol A-glycidyl methacrylate

BMI: body mass index

BPA: bisphenol A

BRIEF-P: Behavior Rating Inventory of Executive Function-Preschool

CAD: coronary artery disease

CBCL: Child Behavior Checklist

CHAMACOS: The Center for the Health Assessment of Mothers and Children of Salinas, Salina, CA.

CHD: coronary heart disease

CMV: cytomegalovirus

CVD: cardiovascular disease

CRP: C-reactive protein

DBP: diastolic blood pressure

DHEAS: dehydroepiandrosterone sulfate

E2: 17-beta estradiol

ECN: embryo cell number

EFS: embryo fragmentation score

EH: endometrial hyperplasia

EPIC-Norfolk Study: The European Prospective Investigation into Cancer and Nutrition Cohort Study, consisting of over 500,000 people (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden and the United Kingdom)

ER: estrogen receptor

FAI: free androgen index (total T divided by SHBG)

FDA: Food and Drug Administration

FSH: follicle stimulating hormone

FT: free testosterone

HbA1c—hemoglobin A1c

hCG: human chorionic gonadotropin

HDL: high-density lipoprotein

HOMES: The Health Outcomes and Measures of the Environment Study (United States)

HRV: heart rate variability

InCHIANTI: A European population representative sample (Chianti, Italy)

IL-6: interleukin-6

ISCI: intracytoplasmic sperm injection

IVF: in vitro fertilization

LDL: low-density lipoprotein

LH: luteinizing hormone

MaGiCAD: The Metabolomics and Genomics in Coronary Artery Disease Study (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden and the United Kingdom)

MDA: malondialdehyde

MGH: Massachusetts General Hospital (United States)

NECAT: The New England Children's Amalgam Trial (United States)

NHANES: National Health and Nutrition Examination Survey (United States)

NNNS: NICU Network Neurobehavioral Scale

OHAT: Office of Health Assessment and Translation

PCOS: polycystic ovary syndrome

PIVUS: The Vasculature in Uppsala Seniors Study (Uppsala, Sweden)

PFOS: perfluorooctane sulfonate

PFOA: perfluorooctanoic acid

rtPCR: reverse transcription polymerase chain reaction

SBP: systolic blood pressure

SCE: sister chromatid exchange

SFF: The Study for Future Families, USA

SHBG: sex hormone binding globulin

SRS: Social Responsiveness Scale

T: total testosterone

T3: triidothyronine

T4: thyroxine

TDI: tolerable daily intake

TSH: thyroid stimulating hormone

UCSF: University of California, San Francisco

USEPA: United Sates Environmental Protection Agency

VCL: curvilinear velocity (μm/s)

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1. Introduction

Bisphenol A (BPA) is a monomer that was first developed as a synthetic estrogen in the 1890s and was reported to have the efficacy of estrone in stimulating the female reproductive system in rats in the 1930s [1]. Subsequently, BPA has been used in many consumer products, including plastics (as a polymer, i.e. polycarbonate [#7] plastic), PVC, food packaging, dental sealants, and thermal receipts. Humans are exposed to BPA through their diet, inhalation of household dust, and dermal exposure [2]. A total of 2.8 million metric tons of BPA was produced in 2002, and an estimated 5.5 million metric tons was produced in 2011 [3]. BPA is a known endocrine disruptor; it has been found to bind to estrogen receptors and have estrogenic effects in laboratory studies. Although BPA has been found to have a lower affinity for nuclear estrogen receptors relative to 17-beta estradiol (E2), its estrogenic potency is equal to E2 for responses mediated by non-nuclear estrogen receptors [4]. Further, BPA can act as an antiestrogen, blocking the estrogenic response by competing with endogenous E2 [5, 6]. BPA can also directly bind to androgen receptors, and is possibly antiandrogenic, blocking endogenous androgen action [7, 8]. BPA has been shown to bind to thyroid receptors, and have both agonistic and antagonistic effects on thyroid function [7, 9]. BPA interacts with other organs and physiological

systems as well, including the developing central nervous system, the endocrine pancreas and the immune system [7]. Determining which of the different molecular mechanisms mediate the effects of BPA on different aspects of human health is the goal of a considerable amount of research [2].

BPA has also been used as one of the most frequent models for demonstrating the low dose and non-monotonic nature of hormones (and EDCs) that regulate or affect the endocrine system [2]. Non-monotonic dose-response curves (NMDRCs) indicate a change in the direction (i.e. sign) of a dose-response curve slope. NMDRCs often follow a "U" or "inverted U" shape. Endogenous hormones often follow these non-linear effects at the low doses present in the body, due to endocrine mechanisms such as binding kinetics and tissue specific actions. The so-called 'low-dose hypothesis' supports the idea that 'low-doses' (i.e. those in the range of typical environmental human exposure) can act in this non-linear manner. There are numerous studies showing BPA can have significant effects at low, environmentally relevant, doses, which may not be apparent at higher doses used in traditional toxicology studies [2]. Thus, determining if there are health effects of BPA on humans, most of whom are exposed to low doses of BPA on a daily basis, is important [10-12].

A large body of evidence (over 300 published studies) links BPA to adverse health effects in mammalian and non-mammalian laboratory, wildlife, and in vitro models [5, 6, 13, 14]. Although this literature supports the assertion that environmental exposure to BPA may be detrimental to human health [13], there is less research examining BPA effects in humans. This is troubling, not only because of the laboratory evidence that suggests BPA can have potent

endocrine disruptive and other effects, but also because exposure to BPA is essentially ubiquitous in humans. BPA is detectable in the urine of almost all adults and children tested [10-12], as well as in the serum of pregnant women [15], breast milk [16], follicular and amniotic fluid [17], cord blood and placental tissue [15], and human fetal livers [18], which indicates BPA exposure is prevalent in utero in developing fetuses. Urinary BPA was also found in comparable concentrations in individuals from both urban and rural areas [11, 19], and in individuals from all countries examined [19-27]. Interestingly, women who spent their entire life in the United States had higher urinary BPA than women who immigrated from Mexico [28]. Because of this widespread and daily exposure, it is essential to determine if BPA is causing adverse health outcomes in humans. However, controlled studies of exposure effects cannot be done on pregnant women and children for ethical reasons. In order to protect human health, we must use animal studies and correlational (epidemiological) studies of human populations to determine possible human health effects due to BPA exposure, particularly during development.

A recent review examined 22 peer-reviewed studies in humans, published between 2002 and April 2011, with a special focus on BPA and children's health outcomes [29]. Since then, however, 53 epidemiologic cross-sectional, prospective cohort, case report, case-control, and randomized clinical trial studies have been published, examining human exposure to BPA (prenatal, childhood, and adult) and adverse reproductive and other health outcomes. Further, there are 16 earlier studies, not mentioned in Braun and Hauser [29]. Sixteen of the total studies show no effects of BPA on the parameters measured (Table 1). Studies were deemed to have significant effects based on p-values; risk estimates of each health effect were not reported in Table 1 due to space limitations. Where effects are noted, all are at $p < 0.05$, unless stated

differently. For example, several studies showed "trends" (i.e. p-values between 0.05-0.1, effects in some statistical tests but not others, or author-determined "weak effects"). In all, to our knowledge, there are currently 90 studies examining BPA and human health effects, as of May 2013 (Table 1). Four of these papers are in Chinese only [30-33], and are listed in Table 1 but not reviewed in this manuscript. One case-study was identified [34]; it is not listed in Table 1, and not reviewed in the current manuscript.

The aim of the literature search was to find all studies examining the associations between BPA exposure and health effects or physiological changes in humans. To that end, a broad search was conducted, utilizing Pubmed, Google Scholar, and Web of Knowledge. In Pubmed, the search term '"Bisphenol A" AND (human OR adult OR child)' was used, which resulted in 4783 articles. The criteria used to select the studies was as follows: 1) study subjects were environmentally (through diet, dermal exposure, dust, dental fillings, etc.) or occupationally exposed to BPA; 2) exposure was measured by blood, urine, environmental sampling, or occupational records; 3) specific health diseases, health outcomes, or physiological changes were measured in the individuals and/or offspring (excluding contact dermatitis); 4) only human in vivo studies were selected. The majority of the search results were chemical analysis/characterization studies, pharmacokinetic/pharmacodynamics studies, animal studies, in vitro studies, and studies that monitored BPA exposure only; these studies were excluded. Also excluded were studies examining BPA and contact dermatitis in humans. Of the total search, 68 articles were selected as appropriate for review from examination of titles and abstracts. A subsequent search in Google Scholar for "'Bisphenol A' and human" was performed in order to find papers that may not be accessible in PubMed [35]. This search found ~28,400 articles,

presented by order of search relevance. The first 100 pages (1000 results) were examined for appropriate studies (the maximum allowable for Google Scholar). Ten additional appropriate articles were found by examining titles and abstracts. Web of Knowledge searches were carried out, using the search terms "Bisphenol A AND cohort," 'Bisphenol A AND case-control,' 'Bisphenol A AND clinical trial,' and 'Bisphenol A AND occupational.' Three additional papers were identified from these searches. Ten articles were found using the reference lists of the final articles, and Braun and Hauser [29], for a total of 91 papers.

Although all the studies that met the above mentioned criteria were included, they were subsequently analyzed for quality according to several parameters, based on the National Toxicology Program Office of Health Assessment and Translation (OHAT) approach, including study design features, possible biases (selection, performance, attrition/exclusion, detection, and selective reporting), statistical methods, sample size, unexplained variation or outcomes, magnitude of effect, dose-response, bias towards the null, biological plausibility, and cross-species/population consistency [36]. Using these parameters, the strength of evidence is discussed for each health effect. The OHAT approach designates confidence ratings for the type of study carried out, with experimental animal and human controlled trials having the highest confidence ratings (based on controlled exposures, exposure prior to outcome, individual outcome data, and comparison groups used). Because many epidemiological study-types (i.e. cohort, case-control, cross-sectional studies) by their nature do not include controlled exposures, and many do not include measured exposures prior to outcome measurements, these studies are inherently less strong in terms of confidence, compared to animal studies and controlled human exposure studies. Further, longitudinal studies are inherently more rigorous than cross-sectional

studies, as they measure the exposure before the outcome [36]. As previously mentioned, however, these epidemiological studies are necessary, in conjunction with animal studies, to understand the potential effects of BPA on human health.

This review outlines the literature-to-date examining the link between human BPA exposure and many adverse perinatal, childhood, and adult health outcomes, including reproductive effects: (A) fertility (i.e. ovarian response, fertilization success, embryo quality, and implantation failure), male sexual function, sperm quality, sex hormone concentrations, endometrial disorders, polycystic ovary syndrome (PCOS), breast cancer, miscarriage, and premature delivery; (B) developmental effects: birth weight, male genital abnormalities, childhood behavior and neurodevelopment, and childhood wheeze; (C) metabolic disease: type-2 diabetes, cardiovascular disease (i.e. heart disease, hypertension, and cholesterol levels), liver function, and obesity; and (D) other health effects: thyroid hormone concentrations, immune function, albuminuria, oxidative stress and inflammation, and epigenetics and gene expression.

2. BPA and Human Health Effects

2.1 Reproduction

2.1.1 Fertility

It has been suggested that environmental chemicals may be impairing human reproduction [37], and BPA has been shown to affect many endpoints of fertility [7]. Several prospective cohort studies examined individuals undergoing infertility treatments (i.e. in vitro fertilization, IVF), and measured BPA in relation to various reproductive endpoints, such as ovarian response, fertilization success, embryo quality, and implantation failure. Ovarian response during the IVF

procedure for oocyte collection is measured by the number of oocytes retrieved and peak serum E2 concentration on the day of hyperstimulation with human chorionic gonadotropin (hCG) [38]. Poor ovarian response has been associated with a decrease in IVF success [39]. In a cohort of women recruited from the Massachusetts General Hospital (MGH) Fertility Center who were undergoing IVF treatments, higher total urinary BPA was associated with a poorer ovarian response (fewer oocytes retrieved per cycle and decreased E2) [39]. In another population of women from the MGH Fertility Center, Ehrlich et al. [38] found that higher urinary BPA again significantly correlated with lower serum E2 and oocyte yield. They also found that higher urinary BPA corresponded to reduced maturation of the oocytes, as measured by the number and percentage of mature oocytes at metaphase II on the day of egg retrieval. There were also fewer normally fertilized oocytes in women with higher urinary BPA, measured by the number and percentage of oocytes with two pronuclei. Fertilized embryos were also examined for normal cell cleavage. There was a trend ($p = 0.08$) for increased urinary BPA to be associated with decreased blastocyst formation on Day 5 of fertilization [38].

Bloom et al. [40] examined a cohort of couples undergoing IVF, recruited from the University of California, San Francisco (UCSF) Center for Reproductive Health. Higher unconjugated serum BPA in the women was associated with lower serum E2 (after hyperstimulation with hCG), and even more strongly associated with lower E2 per mature follicle, a more precise measure of follicular stimulation. In contrast to the previously mentioned studies, Bloom et al. [40] did not find an association between BPA and the number of oocytes retrieved per cycle. The authors stated that measuring unconjugated BPA rather than total BPA may have been a factor in the differing results [40].

Fujimoto et al. [41] studied both Asian American male and female partners from the UCSF cohort. They found a 55% decrease in the probability of fertilization with a doubling of female unconjugated serum BPA, and this was further reduced by 6% with a doubling of male serum BPA, although male BPA exposure alone was not a significant factor. They also found that, in women undergoing ICSI (intracytoplasmic sperm injection), there was a decreased probability of mature oocytes with increased serum BPA. Further, in men, there was a decreased probability of fertilization with higher serum BPA. The authors suggest that ethnicity plays a factor in sensitivity to BPA [41]. There is evidence that disruption of the ovarian response may be at the level of the granulosa cells, via estrogen receptor (ER)beta [38-41].

In a separate study of the UCSF cohort, Bloom et al. [42] found that increased serum BPA in male, but not female, partners was associated with reduced embryo quality, measured by lower embryo cell number (ECN) and increased embryo fragmentation score (EFS). The sample size was small for this study, but suggests a role for sperm quality related to BPA exposure of the father on early reproductive development in the offspring [42]. The evidence that BPA contributes to infertility in men is not strong, however. Indeed, in a large cross-sectional study of men with idiopathic infertility, there was no association between BPA and infertility, although certain octylphenols were significantly associated [43].

Ehrlich et al. [44] examined the MGH cohort in relation to implantation success of IVF embryos. Implantation success was measured in women undergoing IVF, defined as low beta-hCG concentration measured 15-20 days after egg retrieval. The women underwent one of three IVF

protocols. Women with higher urinary BPA had higher implantation failure (unadjusted values), with the highest BPA women having twice the chance of implantation failure. When values were adjusted, the trend continued, but became non-significant (p=0.06). Values adjusted for IVF protocol were also not significant. The authors concluded that women undergoing certain IVF protocols seemed to be more sensitive to BPA exposure [44].

All these studies were appropriately designed and carried out well, but many had low sample sizes (Table 1) and were deemed preliminary by the authors, indicating more work is needed to confirm the results. Further, some of the effects, although statistically significant, were not large in magnitude. However the results were fairly consistent across the population groups, and similar studies were replicated in different populations, corroborating the overall findings. These studies are not necessarily relatable to the general population, since infertile couples and/or couples undergoing IVF may be more sensitive to BPA in regard to these endpoints. However, approximately 1/3 of these women had infertility diagnoses due to the 'female factor,' 1/3 due to the 'male factor,' and 1/3 had unexplained infertility [38-42, 44]. This indicates that neither female nor male infertility alone explains the increased sensitivity to BPA in these populations. Further, Caserta et al. [45] recently published a study that compared infertile women to fertile controls, and found that the infertile women were significantly more likely to have detectable serum BPA, while other chemical exposures (PFOS, PFOA, MEHP, DEHP) were not different between the two groups. This literature indicates that there is some evidence that BPA may contribute to infertility in humans.

2.1.2 Male Sexual Function

Two excellent cohort studies by Li et al. [46, 47] examined self-reported male sexual function in workers. Men working in BPA and epoxy resin manufacturing companies in China and non-exposed men were studied. BPA exposure was determined by reviewing historical records of the factory, carrying out spot air sampling, and performing personal air monitoring. Participants took a general health survey but were not told that the effects of BPA were the targets of the study. Exposed workers had significantly lower self-reported sexual function (i.e. erectile function, orgasmic function, sexual desire, and overall satisfaction with sex life) than controls. Decreased sexual function was related to BPA exposure in a dose-dependent manner [47]. A subset of the same population of workers gave urine samples that were tested for total BPA. Higher urinary BPA was significantly correlated with lower self-reported sexual function (see above). Of note, the control group, who were exposed environmentally but not occupationally, also showed significant negative correlations in a few of the parameters (sexual desire, overall satisfaction with sex life), indicating BPA exposure could reduce male sexual function in the general population, which had lower BPA exposure then the occupational workers [46]. In both studies, a history of exposure to other environmental toxicants was taken. Previous occupational chemical or heavy metal exposure had no impact on the results, indicating that the effects seen were likely not due to past chemical exposures [46, 47]. These studies had several strengths, including documenting the history of BPA production in the participating factories (i.e. long-term exposure), good sample sizes, and the fact that the studies were biased towards the null hypothesis, but still had large magnitude of effects. And in general, occupational studies may be stronger, as exposure is better classified and is likely consistent over the occupational time-

period. The link between BPA exposure and male sexual function would be further strengthened by replication of these findings in another cohort.

2.1.3 Reduced Sperm Quality

Li et al. [23] also examined sperm quality in the men who provided urine samples from the previously mentioned occupational cohort study. Higher urinary BPA was significantly correlated with lower sperm quality measures (i.e. concentration, count, vitality, and motility), again controlling for exposure to other chemicals/metals, and other factors. When only the control group was analyzed (i.e. individuals environmentally, but not occupationally exposed to BPA), there was still a significant negative correlation between urinary BPA and sperm concentration and total sperm count. The median urine total BPA concentration in the occupationally exposed men was 38.7 μg/L, which is ~70x lower than the accepted tolerable daily intake according to the USEPA (i.e. urine levels of 2,678.5 μg/L when exposed to 0.05 mg/kg/day). Further, the median BPA level in the control group was 1.4 μg/L, ~2000x lower than the accepted daily intake [23]. This suggests that BPA may be detrimental at much lower doses than the USEPA accepted daily intake, which is further considered in "Discussion and Conclusions."

Meeker et al. [48] tested sperm quality parameters of sub-fertile couples in the MGH cohort. The authors employed several statistical models, due to some differences in the number and timing of urine samples. When analyzing spot urine samples on the same day of the semen sample, there was a significant correlation with higher urinary BPA and lower sperm count, sperm morphology, sperm motion (VCL), and DNA damage (tail%). Additionally, significant non-

monotonic dose responses were apparent in sperm concentration, sperm motility, and tail%. Although same-day BPA exposure would likely not affect the sperm collected on that day, spot urine samples have been shown to be a good measure of recent exposure to BPA (days to weeks) [49], and thus may be a fairly accurate measure of exposure during sperm development [50]. This study also found that BPA concentration was higher in samples taken in the evening vs. samples taken in the morning. The authors suggest that men with sub-fertility may be more susceptible to BPA-related effects than men with normal fertility [48]. Indeed, Mendiola et al. [51] studied the Study for Future Families (SFF) cohort of fertile men and found higher urinary BPA to be correlated with reduced seminal volume. Although there have only been a few studies relating adult BPA exposure to sperm quality in men, the studies are high-quality, with large sample sizes, strong dose-response effects, and show consistent results in different populations.

2.1.4 Sex Hormone Concentrations

Many studies have found changes in endogenous sex hormone concentrations (i.e. estrogens, androgens, and gonadotropins), as well as sex-hormone binding globulin (SHBG), in relation to BPA exposure in adults and neonates. Hanaoka et al. [52] measured BPA levels in workers exposed to bisphenol A diglycidyl ether (BADGE) and age and smoking-matched controls. The workers exposed to BADGE from spraying epoxy resin had significantly higher total urinary BPA concentrations than controls, and significantly lower follicle-stimulating hormone (FSH). Other urinary metabolites of organic solvents were present in the workers but did not significantly correlate with hormone concentrations [52]. In a cross-sectional study Meeker et al. [53], found that males with , higher total urinary BPA was associated had higher FSH (as opposed to Hanaoka et al. [52]), as well as lower inhibin B. Further, BPA exposure was

associated with a higher FSH:inhibin B ratio, and a lower estradiol:testosterone ratio. According to Meeker et al. [53], the former is associated with poor sperm quality, and the latter indicates BPA may interfere with aromatase activity.

Takeuchi and Tsutsumi [54] tested healthy women and men, as well as women with polycystic ovary syndrome (PCOS) for serum BPA and hormone concentrations. Total testosterone (T) and free testosterone (FT) were significantly higher in men and PCOS women than healthy women. Men also had significantly higher FSH and dehydroepiandrosterone sulfate (DHEAS), and lower E2, than non-PCOS women, while the PCOS women had significantly higher E2, luteinizing hormone (LH), and androstendione. Both PCOS women and men had higher total serum BPA than non-PCOS women. Takeuchi et al. [55] studied sex hormone concentrations in non-obese and obese women, with and without PCOS, as well as women with hyperprolactinemia and women with hypothalamic amenorrhea. In all women, higher serum BPA was positively correlated with total T, FT, androstendione, and the adrenal androgen DHEAS [55]. Kandaraki et al. [56] also found a significant association between BPA and elevated androgen concentrations in women with and without PCOS.

Mendiola et al. [51] studied men involved in the SFF study. They found that increased total urinary BPA was significantly associated with a decreased free androgen index (FAI, i.e. total T divided by SHBG) and decreased FT. The changes in FT were not as large as normal daily changes, however. Increased SHBG was also significantly associated with increased urinary BPA, possibly directly stimulated by the estrogenic action of BPA [51].

In a large cross-sectional study, (the InCHIANTI study), Galloway et al. [19], tested daily urinary excretion of BPA and measured serum E2 and T concentrations in an Italian adult population. Men and younger adults had higher total BPA excretion rates. Higher BPA exposure was associated with higher T in men, but not women. In premenopausal women there was increased SHBG with higher BPA concentrations, but this was not seen in men [19], in contrast to the findings of Mendiola et al. [51]. Zhao et al. [57] found no correlation between BPA and E2 in healthy adult women.

In a study examining cord blood from newborn boys with and without cryptorchidism, Fénichel et al. [58] found that there was a positive correlation in the control babies between unconjugated cord blood BPA and total T as well as inhibin. This was the only study examining BPA-sex hormone associations during the perinatal period [58]. However, another study examined children from areas around the polluted SY River in China. The water from the SY River Basin was contaminated with several endocrine-disrupting chemicals, including BPA. Tang et al. [59] compared E2 and T concentrations in children who were born in areas with highly polluted drinking water to those born in control areas. Children from contaminated areas had significantly lower E2 and T concentrations than the control children. This study, however, did not isolate BPA as specifically correlated with reduced sex hormone concentrations [59].

The studies relating sex hormone concentrations and BPA exposure are, on the whole, strong, with good sample sizes, statistical analyses, and fairly consistent effects across many types of populations and age groups. This supports the idea that BPA has activational effects on circulating levels of sex hormones.

2.1.5 Polycystic Ovary Syndrome

Many studies have related BPA to polycystic ovary syndrome (PCOS) in adult women, although these studies can be difficult to interpret, as elevated androgens are a symptom of PCOS, and also associated with increased BPA. Thus, there is no way to attribute an association solely to either factor, as they are correlated with each other [55]. As described previously, Takeuchi and Tsutsumi [54] and Takeuchi et al. [55], found significantly higher total BPA exposures in women with PCOS. Kandaraki et al. [56] also studied women with and without PCOS, and found that total serum BPA was significantly higher in the PCOS group compared to controls. They also found a significant association between BPA and elevated androgen concentrations. In a study by Tarantino et al. [60], premenopausal PCOS women had significantly higher total serum BPA than controls. BPA was also higher in subjects with increased spleen size (an indicator of inflammation). PCOS women with serum BPA higher than 0.45 μg/L had increased androgen concentrations (the range of detection was 0.3-100 μg/L). FAI and spleen size were determined to be the strongest predictors of BPA concentrations [60]. These studies appear to be very consistent, with PCOS strongly associated with higher BPA. Again, however, it is unclear whether BPA has a role in causing the disorder, or whether it is increased due to increased androgen concentrations in PCOS women [54, 55]. These studies had very strong associations (i.e. large magnitudes of effects), even though a few had low samples sizes (Table 1). Further, they showed very consistent results across several types of populations. Although these studies showed positive effects, they did not measure previous exposures, and it is known that PCOS develops over a long period of time [61]. Thus, it will be important to determine if early or in utero exposure to BPA has a role in the adult onset of PCOS [62], as indicated by rodent studies

[63]. Further animal and human studies should be carried out, monitoring prenatal BPA exposure and the later development of PCOS in women.

It is unclear why BPA seems to be associated with increased T in men and women (with and without PCOS) and newborns. BPA possibly stimulates T production. BPA has been shown to inhibit T hydroxylase activity, thus leading to increased T concentrations [64]. Also, BPA has been shown to increase T production in the ovary [65]. However, because this association seems to occur consistently in men and PCOS women, higher T may conversely cause increased BPA concentrations, possibly by reducing BPA metabolism and excretion from the body, via reduction in liver enzymes [66].

2.1.6 Endometrial Disorders

Endometrial disorders in adult women have been associated with BPA exposure, although the evidence in humans is not strong. In a small case-control study, Cobellis et al. [67] tested women with and without endometriosis for total BPA exposure. Serum BPA was not detectable in any of the controls (N = 11), but was detected in 52.7% of the individuals with endometriosis (N = 58), when the limit of quantification was 0.5 μg/L. No statistics were run on these data [67]; however, an analysis of the data presented found a significant increase in the likelihood of total serum BPA in women with endometriosis in this study (Fisher's exact test, $p < 0.01$). Hiroi et al. [68] also carried out a case-control study, in which they included a small sample of women with simple endometrial hyperplasia (EH), complex EH, endometrial cancer, and healthy controls. Unexpectedly, serum BPA was significantly lower in complex EH patients, compared to simple EH patients, and, in endometrial cancer patients, serum BPA was significantly lower than in both

simple EH patients and controls. These results show a significant association between BPA and EH and endometrial cancer, but the relationship was surprisingly negative. Thus, the authors conclude that the associations between BPA and EH may be complex [68].

Lastly, Itoh et al. [21] examined a cross sectional population of infertile women. Total urinary BPA was measured, and the severity of endometriosis diagnosed. There was a trend for higher BPA correlating with more severe endometriosis ($p = 0.08$), but this became null after adjusting for urinary creatinine, which adjusts for the urine dilution. The authors concluded that there was no relationship between endometriosis and BPA [21].

In sum, the literature does not seem to support the relationship between BPA and endometrial disorders. The studies have inconsistencies regarding the relationship of BPA to endometrial disorders, small sample sizes, and a lack of statistical support. Since these were all adult studies, it is unclear whether early or in utero exposure to BPA could induce endometrial disorders/diseases in adulthood, as has been shown in rodents [69].

2.1.7 Breast Cancer

In a study of the associations between BPA and cancer in humans, Yang et al. [70] analyzed total serum BPA from women with and without breast cancer. There was a non-significant elevation of BPA in the cancer patients [70]. Another study found no association between adult occupational exposure (as measured by survey) to BPA and breast cancer diagnosis, although the sample sizes were also very small [25 cases; 71]. Based on these studies, a link between BPA and breast cancer cannot be determined. A more biologically relevant study design may be

longitudinal studies measuring BPA in utero, as breast cancer most likely takes years to develop, and may even be established in the womb [72]. These studies are expensive and time-consuming, however, and we may have to rely on animal studies to answer these questions. Indeed, there is ample evidence from rodent [73-85] and primate [86] studies that prenatal exposure to BPA causes disruption of the mammary tissue and increases susceptibility of the tissue to chemical carcinogens.

2.1.8 Miscarriage

There is some evidence of a relationship between recurrent miscarriage and BPA exposure in women (Table 1). Sugiura-Ogasawara et al. [87] studied patients who had 3 to 11 consecutive miscarriages and healthy controls. Women who experienced recurrent miscarriages had significantly higher total serum BPA than the healthy controls from the same town. Further, thirteen karyotypes of the miscarried conceptus were analyzed, and there was a trend of higher BPA in the women with abnormal embryos. Serum BPA was also higher in the miscarriage patients with higher concentrations of antinuclear antibodies (ANAs). Higher ANAs are associated with autoimmune diseases. Of the miscarriage patients who subsequently had successful pregnancies, there was a trend of less serum BPA, but this was not significant [87]. Although there were significant effects, this study had a small sample size, and was deemed preliminary by the authors; more studies are needed to confirm these results. It was well designed, with careful selection of the subjects and analysis of several other health factors (immunological tests, thyroid function, and metabolic disease parameters) [87]. Further, the mechanisms are biologically plausible. While there are several possible causes of miscarriage, including lack of endocrine support [88], the authors of this paper suggest that increased

incidence of miscarriage from BPA exposure may be due to an increase in chromosomal abnormalities of the oocytes due to meiotic disruption, which has been shown in mice [87, 89, 90].

2.1.9 Premature Deliveries

BPA has also been associated with shorter gestation time and premature delivery in one study. Cantonwine et al. [20] collected spot urine samples during the third trimester of pregnancy in a population of Mexican women. There was a significant association between elevated total BPA and premature delivery (<37 weeks), although the sample size for the individuals in this category was small (N=12). When delivery at 37 weeks was included in the premature category (to increase sample size), there was a trend towards significance ($p<0.08$). Although the sample size was small for this study, there were several strengths, including bias toward the null, and sampling for another chemical exposure [20]. Another study found no differences between BPA and gestation length [91].

2.2 Development

2.2.1 Birth Weight

Miao et al. [92] retrospectively studied the birth weight of children in relation to the parents' exposure to BPA in exposed and non-exposed workers (the same population as Li et al. [2010a, 2010b, 2011]). The birth weights of single children from mothers or fathers exposed (or not exposed) occupationally to BPA were reported. Children with exposed mothers had significantly lower birth weight than children of unexposed mothers, and children with exposed fathers also had lower birth weight, although this was not significant. There was a significant linear dose-

response relationship (on a continuum of high exposed mothers to low exposed fathers) between higher BPA exposure and lower birth weight, indicating biological plausibility [92]. One pitfall of this study was possible detection bias in the outcome assessment—i.e. parents may have had recall error when reporting birth weight. There is no reason to suspect, however, that exposed parents would err toward reporting lower birth weights than the birth weights reported by unexposed parents. In addition, the authors cite previously reported high validity of parental recall of birth weight [93], as well as increased accuracy because of single children [92]. In a separate study by Miao et al. [94] examining a subset of the same population, sons of exposed parents also had slightly lower birth weight than unexposed sons, although statistics were not run on these data.

In a French case-control study of mother-child cohorts, Philippat et al. [25] found a positive association between maternal BPA and birth weight/size, and increased head circumference with higher maternal urinary BPA. They also found a suggestion of an inverse U-shaped (i.e. non-monotonic) association between birth weight and maternal urinary BPA, with the mid-range exposures associated with increased weight of newborns [25].

Chou et al. [95] also found non-monotonic effects of maternal BPA exposure on birth weight and other outcomes in infants. The authors measured serum BPA of pregnant women at the time of delivery. They found that higher maternal BPA significantly increased the risk of having a male infant with low birth weight (LBW); however, this association followed a Z-shaped curve, with higher risk of LBW in the mid-low and highest maternal BPA exposures. A similar non-linear association was seen in male and female infants when the authors measured the risk of smaller

size for gestational age (SGA). Male infants followed a U-shaped curve, while female infants followed a Z-shaped curve. In both cases, the highest maternal BPA exposure significantly correlated with increased risk of SGA. The authors also found increases in adipokine secretion in infants from mothers with higher BPA exposures. In general, higher maternal BPA correlated with negative birth outcomes in this study, particularly in male infants [95].

Earlier studies did not find an association between birth weight and maternal BPA exposure in utero. Wolff et al. [96] tested for a variety of phenols and phthalates in maternal urine, and did not find significant associations between BPA and birth size. No correlation between newborn birth weight and maternal BPA exposure (serum BPA) was detected in another 2008 study [91].

These five studies had diverging results, including negative associations, positive associations, and no effects. Although the general quality of all the studies was good (i.e. appropriate statistics, exposure and outcome assessment measures, etc.) the design differed between each study, possibly resulting in the conflicting findings. Miao et al. [92] found a large magnitude of effect in their study. Although the exact exposure levels were not measured, the subjects were occupationally exposed at BPA-producing manufacturing plants, indicating relatively high exposure. [92]. Padmanabhan et al. [91] and Chou et al. [95] both analyzed serum BPA collected at delivery, in relation to birth weight, although the former found no effect and the latter found a negative effect of BPA [36]. Chou et al. [95] measured total BPA, while Padmanabhan et al. [91] measured unconjugated BPA, which may have contributed to the differing results. Lastly, Philippat et al. [25] and Wolff et al. [96] measured urinary BPA during mid to late gestation, and had differing results (i.e. a positive association between BPA exposure and head circumference,

versus no effect). There were a few differences in the design and exposure that may have accounted for this. For example, Philippat et al. [25] measured BPA slightly earlier than Wolff et al. [96] (24-30 weeks gestation vs. 25-40 weeks). The exposures were also slightly different, with the average high exposure being higher in the Philippat et al. [25] study than the Wolff et al. [96] study.

To sum, the evidence of BPA affecting birth weight is equivocal. Clearly, the literature does not support a clear-cut link between prenatal BPA exposure and altered birth weight of the offspring. More studies, examining exposures at several time points during gestation, are needed.

2.2.2 Male Genital Abnormalities

Male genital abnormalities, such as shorter anogenital distance (AGD), have been associated with exposure to antiandrogenic endocrine disruptors in humans [97]. In the previously mentioned study, Miao et al. [94] measured the AGD of sons, aged 0-17 years, from parents occupationally exposed and non-exposed to BPA (researchers were blind to the exposure group of the parents). AGD was adjusted for weight and height, and pre-pubertal and post-pubertal boys were grouped separately. Boys from BPA exposed parents had shorter AGDs, and boys from exposed mothers had a statistically significant correlation to BPA exposure, in both pre- and post-pubertal analyses. There was also a strong linear dose-response relationship, with higher BPA exposure showing shorter anogenital distances in sons, indicating BPA had antiandrogenic effects in utero [94]. This study had a good sample size, good assessment and analytical techniques, a large magnitude of effect, and a linear dose-response in the expected direction. Further, the study was biased toward the null, increasing the weight of the findings.

Adjusted AGD remains constant in rodents (and possibly humans) persisting through puberty, and thus is a very useful endpoint for in utero exposure to antiandrogenic chemicals [98]. Similarly, shorter adjusted AGD may indicate antiandrogenic exposures during embryonic development in humans [99], and the current study indicates that the relative AGD may persist through childhood and the post-pubertal period [94], although more studies need to be done to verify this endpoint in humans.

Another male genital abnormality, cryptorchidism, was not found to be associated with developmental BPA exposure in newborn boys, measured in cord blood, but the authors expressed concern for other developmental diseases, as they found nanomolar concentrations of BPA in the cord blood of newborns, levels similar to those that cause adverse effects in rodents [58]. Neither cryptorchidism nor hypospadias in newborn boys were found to be associated with in utero exposure to BPA (measured in maternal urine) in another case-controlled study, although it is unclear when during gestation the maternal urine samples were collected [100]. Similarly, Brucker-Davis [101] found no association between BPA and cryptorchidism. These studies were fairly strong, with good sample sizes, assessment techniques, and statistical analysis, thus supporting the null outcome. Based on the current evidence, there does not seem to be a link between BPA exposure and cryptorchidism. Because antiandrogenic endpoints have been linked to prenatal BPA exposure (i.e. AGD), it has been suggested that the antiandrogenic activity of BPA may be through non-classical (ER/AR-mediated) mechanisms, and thus certain endpoints may not be affected [58].

2.2.3 Childhood Behavior/Neurodevelopment

Several recent studies have reported altered behavior in children exposed to BPA in utero or before puberty, indicating disruption of the brain during critical developmental windows. Longitudinal studies such as these are much stronger than cross-sectional studies that measure exposure at the same time as the outcome; the parameter of 'exposure prior to outcome' increases the quality of the study design [36]. Further, there is ample evidence that the propensity to develop certain diseases from environmental factors is established prenatally or early postnatally [102]. Thus, it is likely that EDCs have a greater effect on human health when exposure occurs during gestation or in the early postnatal years.

Braun et al. [103], in a prospective cohort study (the Health Outcomes and Measures of the Environment Study, HOMES), tested pregnant women for total urinary BPA at approximately 16 and 24 weeks of gestation, and around the time of birth. When the offspring were 2 years of age, their behavior was evaluated using the validated Behavioral Assessment System for Children (BASC-2) Parent Rating Scale for preschoolers, which is a parent-reported "assessment of a child's adaptive and problem behaviors in community and home settings" [103]. In girls, but not boys, there were significant associations between higher maternal BPA and increased externalizing behaviors (i.e. hyperactivity and aggression) as well as poorer scores on the "Behavior Symptom Index" at 2 years of age. BPA concentrations from samples collected at 16 weeks gestation correlated more strongly with the externalizing scores in all children, particularly in girls. This association was especially strong at ≤16 weeks, indicating a possible critical time frame for exposure [103]. Braun et al. [10] then followed these children, assessing behavior at 3 years of age and collecting urine from the children at 1, 2, and 3 years old. Each

10-fold increase in maternal urinary BPA was associated with more anxious and depressed behavior (on the BASC-2 scale) and poorer emotional control (in another behavioral assessment, Behavior Rating Inventory of Executive Function-Preschool [BRIEF-P]). Again, these associations were stronger in girls, and non-significant in boys. Further, these associations were only significant for prenatal BPA exposure; while childhood BPA concentrations were not associated with altered behavior [10]. These studies together indicate disruption of neurodevelopment caused by in utero BPA exposure, especially in girls, that seem to have long lasting effects.

In contrast, Yolton et al. [104] used the HOMES cohort to assess 5-week old infant neurobehaviors, using the NICU Network Neurobehavioral Scale (NNNS). They found no correlation between maternal BPA and infant neurobehavioral abnormalities. Notably, BPA concentrations in the maternal samples were lower than nationally reported concentrations; the authors suggest the exposures were below the threshold of neurobehavioral effects in infants [104].

In another prospective cohort study, Perera et al. [105] followed African-American and Dominican women and their children in the United States. Spot urine samples were collected from mothers at ~34 weeks gestation, and from children 3-4 years of age. Child behavior was assessed at 3-5 years of age using the Child Behavior Checklist (CBCL). High maternal total urinary BPA was significantly associated with higher scores (i.e. more problems) for boys in the categories of Emotionally Reactive, and Aggressive Behavior, with trends of poorer scores in Withdrawn and Sleep Problems. In girls, higher prenatal BPA was associated with lower scores

(i.e. less problems) in general, with significance in Anxious/Depressed and Aggressive Behavior. These results differ from the Braun et al. studies [10, 103], which found girls to have poorer scores than boys in association with BPA. Perera et al. [105] suggest that socio-economic/ethnicity differences might be a factor.

In an interesting series of studies, resin-based dental composite fillings were found to possibly affect behavior in prepubertal children [106-109]. Composite fillings contain BPA, and have been shown to leach BPA immediately after the filling procedure [110], and may possibly leach long-term [111]. The studies all stem from the New England Children's Amalgam Trial (NECAT), a randomized clinical trial conducted from 1997-2006. The trial was designed to discover any adverse health effects from amalgam (mercury) fillings, and composite fillings were used as a control. Children (N=534, ages 6-10 years old) with two or more tooth caries were randomly assigned treatment with amalgam or resin-based composites. Initial (pre-treatment) testing and follow-ups for up to five years measured behavioral outcomes (i.e. tests of intelligence, achievement, language, memory, learning, visual-spatial skills, fine motor function, problem solving, attention, and executive function), as well as psychosocial measurements. Bellinger et al. [106] found no change in neuropsychological function for children with amalgam fillings between the initial and follow-up testing. However, the children with composite fillings had significantly worse outcomes in two memory tests ('finger windows' and 'number-letter memory') in the follow-up testing [106]. Bellinger et al. [107] also tested the psychosocial status of these children. Children were tested using the parent-administered Child Behavior Checklist (CBCL) before and 5 years after dental treatments. Children with composite treatments had significantly poorer scores in internalizing behaviors, total problem behaviors, activities, and

delinquent behaviors, and generally had poorer scores overall, compared to the children with amalgam fillings [107]. These studies were not specifically looking for detrimental effects of composite fillings, but found that they may be worse than amalgam fillings in terms of changes in the brain and behavior of young children.

Because of these results, Maserejian et al. [108] sought to further examine the possible adverse effects of composite fillings, using the data from the NECAT. They found generally poorer (but non-significant) scores in tests for intelligence, achievement and memory in children with composite fillings compared to amalgam. There were significantly poorer scores in letter fluency, color naming, and in some measures of executive function. They concluded that resin dental composites are associated with slightly poorer tests of neurophysiological development [108]. Maserejian et al. [109] further studied psychosocial behavior from children in the NECAT that had amalgam, bisphenol A-glycidyl methacrylate (bisGMA)-based composite, and/or urethane dimethacrylate-based polyacid-modified composite (compomer) fillings. The composite fillings contain BPA, while the compomer fillings do not. Psychosocial function tests were given at initiation and at a 5-year follow-up time point. Children with increased exposure to bisGMA-based composite fillings reported significantly higher anxiety, depression, social stress, and interpersonal-relation problems compared to children with amalgam or compomer fillings. Interestingly, individuals with more exposure to composites on chewing surfaces had significantly poorer psychosocial outcomes, indicating that exposure may be higher due to degradation of the composite fillings [109]. Although these studies indicate BPA-containing composite fillings may cause detrimental effects for early neurodevelopment in children, it is

unclear if these effects are due to exposure to BPA specifically, or some other feature of the composite fillings.

Lastly, in a study examining older children, Miodovnik et al. [112] studied mother/child pairs in a prospective cohort (Mount Sinai Children's Environmental Health study). Maternal urine samples (collected at 25 and 40 weeks of gestation) were tested for both BPA and phthalates. At 7-9 years of age, the children were assessed for autistic behaviors with the Social Responsiveness Scale (SRS). They found a non-significant negative association between maternal urinary BPA and total SRS score. However, the women in this study also had lower BPA exposures than the nationally reported concentrations, including concentrations near the limit of detection, and the authors caution that this may have weakened the association between BPA and poor social behaviors in children. Indeed, when 6 outliers were removed (from a total sample size of 137), there was a strong significant association [112].

These neurobehavioral studies were high quality and extremely rigorous, collecting samples across several time points during gestation, examining multiple endpoints, and applying appropriate statistical analysis. Similar results with longitudinal follow-up studies on the same population of children also strengthen the findings of long-term effects of early BPA exposure. There were, however, a few pitfalls, discussed by the authors: several of the studies examined inner-city populations of women, and/or populations living in certain housing conditions [10, 103-105, 112]. In these cases, there is possibly a selection bias towards low-income individuals, and increased behavioral problems in the children. However, other factors (such as education level) were not indicative of low socioeconomic status. It is important to note that other stressors,

such as air pollution in the urban environment, can cause neurobehavioral deficits in children [113], which might be confounds in the studies examining urban populations. Although general air pollution was not adjusted for, tobacco exposure, depression in the mothers, income level and other potential stressors were included in the analyses of the urban cohorts. This is a limitation of longitudinal studies—cohorts most likely have common exposure to stressors as well as environmental chemical exposures, based on where they live. Also, a pitfall of the dental filling studies was that they did not examine BPA exposures directly, so it is unclear if BPA alone is responsible for the behavioral effects [106-109]. On the whole, however, the studies strongly suggest that BPA is associated with neurobehavioral problems in children.

2.2.4 Childhood Asthma/Wheeze

Another developmental endpoint that has recently been studied in association with prenatal BPA exposure in humans is childhood wheeze and asthma. Spanier et al. [114] used the prospective birth cohort HOMES data to examine prenatal maternal BPA (at 16 weeks, 26 weeks, and birth) and subsequent wheeze in the offspring. Every 6 months until 3 years of age, parents reported instances of the child wheezing or whistling in the chest. The study was designed to examine the effects of BPA, although other confounds were measured. Tobacco exposure (through blood cotinine) was controlled in the analyses. Although air pollution was not measured, subjects were classified as living in urban, suburban, and rural environments. Other factors that might contribute to asthma (exposure to cockroaches, pets, etc.) were also controlled. Higher prenatal BPA exposure was associated with increased odds of wheeze in the child at 6 months of age, but this association was diminished by 3 years of age. BPA exposure was associated with wheeze at 16 weeks but not 26 weeks of gestation or at birth, signifying a possible critical window of

exposure early in gestation [114]. Donohue et al. [115] examined late prenatal (third trimester) and childhood BPA exposure and development of asthma at 5-12 years of age in a population of African-American and Dominican mother-infant pairs. This study controlled for tobacco smoke exposure, but not air pollution. They found that BPA exposure at 3, 5, and 7 years old (assessed via total urinary BPA) correlated with asthma at 5-12 years of age, and that BPA exposure at 3 years old was associated with wheeze at 5 and 6 years old. Interestingly, prenatal BPA exposure (measured in the third trimester) was associated with decreased risk of asthma at 5 years old. While Donohue et al. [115] did not find associations between prenatal exposure and asthma/wheeze, contrary to Spanier et al. [114], it is important to point out that Spanier et al. [114] found the association with exposure at 16 weeks, not later in gestation. This suggests that there may be prenatal and postnatal windows of susceptibility, which may change the magnitude/direction of the health effect. Prenatal BPA exposure has also been shown to induce asthma in mouse pups [116]. These studies were both high quality, and supported the role of BPA exposure in the development of asthma both prenatally and postnatally. Additional longitudinal studies with different populations are needed to further verify this link.

2.3 Metabolic Disease

2.3.1 Type-2 Diabetes

Type-2 Diabetes has been associated with BPA in many human studies. In the first study examining the link between BPA and diabetes in humans, Lang et al. [117] examined data from a cross-sectional population of American individuals participating in the National Health and Nutrition Examination Survey (NHANES) 2003-2004. Adults 18-74 years old were asked if they were ever medically diagnosed with certain diseases, such as diabetes. Serum analysis was also

carried out, which included blood glucose. The authors found that higher total urinary BPA was significantly associated with increased diagnosis of type-2 diabetes; adjustment for other chemical exposures did not change the observed outcomes [117]. Measured glucose did not significantly correlate with BPA concentrations [117], suggesting that diabetes medications may alter glucose to show no correlation with diagnosed type-2 diabetes [24]. Using the same NHANES data, and including the 2005-2006 data, Melzer et al. [118] also looked at reported diabetes in relation to urinary BPA concentration. They corroborated the significant association found by Lang et al. [117] in the 2003-2004 population, but did not find a significant association in the 2005-2006 population. BPA concentrations were lower in 2005-2006, which might explain a weaker association. However, higher urinary BPA concentrations were associated with diabetes diagnosis in pooled samples of all years [118]. Shankar and Teppala [119] used NHANES data from 2003-2008, examining participants more than 20 years old who were already diagnosed with diabetes. Serum glucose endpoints were analyzed, as opposed to self-reported diabetes in the previous studies. Higher urinary BPA was strongly associated with increased type-2 diabetes (defined as fasting serum glucose greater than 126 mg/dl, non-fasting greater than 200 mg/dl, glycosylated hemoglobin greater than 6.5%, or self-reported hypoglycemic medication or insulin). This positive association between BPA and diabetes was present among normal weight and overweight/obese patients, and smokers as well as non-smokers [119]. Lastly, Silver et al. [120] also used the NHANES 2003-2008 data to examine type-2 diabetes in relation to urinary BPA. They defined type-2 diabetes in individuals by self-reported use of diabetes medication. They also measured hemoglobin A1c (HbA1c), which may be a more accurate measure of type-2 diabetes than fasting glucose. They found that higher urinary BPA was significantly associated with an increased incidence of type-2 diabetes, as well

as increased levels of HbA1c in the blood. These significant associations, however, were driven by only one study cycle (2003-2004) [120].

The NHANES studies are strong in that they provide a robust sample size, follow a standardized methodology, and can control for many demographic and other factors [117-120]. Further, the magnitudes of the effects are generally large, and the affected outcomes are specific. They do have some limitations, however. The cross-sectional nature of the study makes it inherently less rigorous than a prospective cohort study [36]; only adult exposures and outcomes were measured. However, the fact that many independent studies were done with the data with corroborating results further strengthens the association between adult BPA exposure and type-2 diabetes.

In another study, Ning et al. [24] assessed Chinese adults. Higher urinary BPA was non-significantly associated with increased diabetes, as measured by blood glucose, with the odds of having type-2 diabetes slightly increased in the second and fourth quartile of BPA exposure, but not the third. The authors stated that their study did not support an association of total BPA and diabetes. This study had a large sample size, and was generally strong. However, a potential flaw highlighted by the authors was that, because 1087 individuals in the study were being treated for diabetes, blood glucose levels may have been be skewed (lowered) in these individuals, and thus the overall the association of BPA and glucose may have been diluted [24]. It is also possible that ethnicity plays a role in the relationship between BPA exposure in adults and type-2 diabetes, as a cross-sectional Korean study also saw no relationship between BPA and diagnosis of diabetes. However, in this study diabetes was assessed through self-reporting exclusively,

which may under-represent the actual prevalence of diabetes [22]. Other studies from Asian countries reported significant associations between BPA and insulin resistance [121, 122].

Hong et al. [121] studied a large population of adults in Korea, and found, along with other endpoints, a significant association between increased insulin resistance and higher total urinary BPA. They also measured exposure to several phthalate compounds, and found an association between one phthalate, MEHP, and increased insulin resistance (i.e. increased blood sugar), indicating BPA may not be solely responsible for the health outcome [121]. Others have found similar results. In the previously mentioned study, Kandakari et al. [56] found serum BPA was positively correlated with less sensitivity to insulin. Wang et al. [122], in a large study of Chinese adults, found that increased urinary BPA was significantly associated with increased insulin resistance. Finally, Tarantino et al. [60], in the previously mentioned study, found that PCOS women with serum BPA higher than 0.45 ng/ml also had more severe insulin resistance, indicating a 'different subgroup of PCOS women' with more severe adverse health outcomes and higher BPA exposures.

2.3.2 Cardiovascular Disease, Hypertension, and Cholesterol Levels

Cardiovascular disorders and hypertension are other adult onset diseases that have been associated with adult BPA exposure. Much of the literature in this area stems from the NHANES data [117, 118, 123, 124]. Lang et al. [117], in the previous study, found that higher urinary BPA was associated with a more frequent diagnosis of cardiovascular disease (CVD; i.e. angina, coronary heart attack, and heart attack). Melzer et al. [118] assessed individuals 18-74 years of age and found a significant increase in cardiovascular disease (i.e. myocardial infarction, angina,

coronary heart disease [CHD], CVD) with increased urinary BPA in the 2003-2004 data, but in the 2005-2006 data, the only significant cardiovascular endpoint was increased myocardial infarction (or CHD, depending on models). However, pooled data were significant in all categories [118]. Shankar et al. [124] found that higher urinary BPA was significantly associated with increased prevalence of peripheral arterial disease in adults.

In a separate paper, Shankar and Teppala [123] identified individuals that were diagnosed with hypertension, either by blood pressure measurements or if they were reported to be on blood pressure-reducing medication. Higher total urinary BPA was associated with increased incidence of hypertension, independent of confounding factors [123]. Bae et al. [125] also found that increased urinary BPA was positively associated with hypertension in Korean adults. Further, they found that BPA exposure is also associated with reduced heart rate variability (HRV). HRV is important for 'fine tuning' the action of the heart to correspond with blood demand in the body. Decreased HRV and increased blood pressure are both risk factors for cardiovascular diseases [125].

Melzer et al. [126] studied individuals participating in the Metabolomics and Genomics in Coronary Artery Disease (MaGiCAD) study. They found that individuals with severe and intermediate coronary artery disease (CAD) had significantly higher total urinary BPA compared to the normal controls [126]. Melzer et al. [27] further studied individuals with CAD in a nested, case-control, longitudinal (prospective) study, the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk cohort study. The authors identified individuals with CAD and controls, aged 40-74, and followed them for 10.8 years. They assessed urinary BPA from a

single early urine sample, taken at study enrollment. They found that higher urinary BPA from these early samples was positively associated with higher incidence of CAD during 10.8 years of follow-up, indicating early adult exposure may have long-term effects [27].

Olsen et al. [127] found weaker connections between BPA exposure and CHD. The authors studied 70-year old individuals from a cross-sectional study from the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS). Although they found that higher total serum BPA was associated with higher low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol levels, this significance was reduced when correcting for multiple tests. Other factors of coronary heart disease risk (i.e. triglycerides, body mass index [BMI], systolic blood pressure [SBP], diastolic blood pressure [DBP], glucose concentrations) did not appear to be associated with BPA exposure [127].

Again, the NHANES data has its limitations, but on the whole it is strong. The multivariate-adjusted magnitudes of effects were generally large, and several independent laboratories corroborated outcomes. It is interesting to note that in the NHANES studies that surveyed participants' reported health outcomes there were significant associations of elevated urinary BPA and with coronary heart disease (as well as diabetes), but with no other diseases or disorders reported by the participants. The fact that only these outcomes were significant suggests specificity of BPA as a cause of cardiovascular health problems [117, 118]. The other studies examining cardiovascular diseases were also strong, with large sample sizes and strong assessment and analytical methods [27, 125-127]. They largely measured physiological endpoints (rather than just surveying doctor diagnoses), which strengthens the findings. On the

whole, there is strong evidence that adult exposure to BPA is associated with cardiovascular diseases and adverse cardiovascular health, in many populations.

2.3.3 Liver Function

Lang et al. [117] and Melzer et al. [118] found liver function to be altered in adults with higher total urinary BPA concentrations. In Lang et al. [117], which examined the NHANES 2003-2004 data, found higher urinary BPA to be significantly correlated with elevations in the liver enzymes alkaline phosphatase, gamma-glutamyltransferase, and lactate dehydrogenase. Melzer et al. [118] found weaker associations with these three enzymes and urinary BPA, because the NHANES 2005-2006 study did not show significant associations between total urinary BPA and liver enzymes. However, when the data from this study were pooled, there were still significant elevations of alkaline phosphatase and lactate dehydrogenase in association with elevated urinary BPA. Perhaps the lower urinary BPA concentrations, reported in the NHANES 2005-2006 study, may have accounted for weaker associations [118].

2.3.4 Obesity

Body mass index (BMI) and obesity are two of the most studied endpoints with regard to human health and BPA. In the previously mentioned study, Takeuchi et al. [55] found increased BPA was associated with increased BMI in non-PCOS women. They found that obese controls had higher serum BPA concentrations than non-obese controls [55]. In their earlier study, however, there was no association between BMI and serum BPA [54].

In a cross-sectional study, Wolff et al. [128] assessed a subset of girls (6-8 years old) enrolled in the Puberty Study, a multi-site epidemiological cohort of more than 1,200 US girls. "The Puberty Study" is part of the Breast Cancer and the Environment Research Centers (BCERC) research on the determinants of pubertal maturation. Girls in the 85th or higher percentile for BMI had significantly lower urinary BPA, with no associations with many other endocrine disruptors measured (with the exception of enterolactone). This study had a low sample size, possibly weakening the findings [128].

Several NHANES studies found associations of urinary BPA and BMI/obesity. Carwile and Michels [129] examined data from NHANES 2003-2006 participants, and found higher urinary BPA was significantly associated with higher BMI and waist circumference, indicating associations with both general and central obesity. Shankar et al. [130] studied NHANES 2003-2008 participants greater than 20 years old. In this study, higher urinary BPA was strongly associated with higher BMI and waist circumference, as a whole, and when analyzed in subgroups of gender and race/ethnicity [130]. Trasande et al. [131] studied childhood obesity in the NHANES 2003-2004 population, examining children ages 6-19 years. Again, higher urinary BPA was associated with obesity. However, when race/ethnicity was examined the relationship between high BPA and obesity was only seen in Caucasians. Further, non-monotonicity was seen, with the highest quartile having a lower prevalence of obesity [131].

Wang et al. [132] looked at childhood BMI/obesity in a cross-sectional study of Chinese school children, ages 8-15 years. There was a significant association between higher total urinary BPA and higher BMI, especially in the 8-11 year olds. When adjusted for specific gravity to account

for urine dilution, the associations were less significant in specific age groups, but still remained overall [132].

In a study examining mother-child pairs in the CHAMACOS cohort (a longitudinal birth cohort consisting of farmworkers in the Sainas Valley, CA), Harley et al. [133] measured prenatal and postnatal BPA exposure and its association to BMI and body fat in children. In girls, they found that increased prenatal exposure to BPA (measured by total maternal urinary BPA during gestation) was associated with decreased BMI and body fat at 9 years old. However, total BPA measured in the urine of 9-year-old boys was positively associated with increased BMI, waist circumference, fat mass, and overweight/obesity. The authors stress that it is possible the association of BMI and prenatal/postnatal BPA exposure in both boys and girls may change post-pubertally, and measurements should be taken as the children age [133].

In a previously mentioned study, Wang et al. [122] found increased urinary BPA was significantly associated with increased BMI and waist circumference in individuals 40 and older. Galloway et al. [19], also found higher BPA excretion rates among individuals with increasing weight/waist size in their study.

Lastly, Zhao et al. [57] in a cross-sectional study of healthy, premenopausal, non-obese, Chinese women, ages 20-55, urinary BPA was positively associated with body weight, BMI, fat mass, and serum leptin concentrations. It is interesting to note that this study population was non-obese, indicating that BPA may be elevated with increased BMI even in healthy individuals [57].

Several of the studies described in other sections did not find associations between BPA and BMI/obesity, although some found other adverse health effects [49, 56, 60, 117]. Additionally, Wolff et al. [96] found a weak positive association between urinary BPA and BMI in pregnant women. In a paper describing outcomes from the NECAT, children with dental composite fillings (which contain BPA) had no changes in BMI, body fat percentage, or rate of growth over a 5 year follow-up period, compared to children with amalgam fillings [134].

The positive associations between BPA exposure and BMI/obesity are difficult to interpret, and the cross-sectional nature of these studies do not allow for causal links. It is possible that the increased BPA seen in these individuals is due to increased body fat, instead of BPA inducing increased BMI. However, in an in vitro study of human adipose tissue, there was no association between BMI and adipose tissue BPA concentration, indicating that increased urinary or serum BPA is not due to increased adipose stores of BPA [135]. It is also possible that individuals with increased BMI have higher caloric intake and may be exposed to higher concentrations of BPA through food packaging or other lifestyle factors. However, Trasande et al. [131] found an inverse relationship between caloric intake and BMI in their study. Although this might indicate underreporting, it could also be a product of reduced caloric intake due to weight management [131], indicating increased BPA is not due to increased food intake. It has been suggested that BPA increases BMI by causing insulin resistance [136], altering the adiponectin release from adipose tissue [137], and increased inflammatory cytokines [138]. Further, in utero exposure BPA has been shown to induce postnatal weight gain in rodents [139, 140], although it is unclear if adult exposure induces weight gain in rodents [141]. The fact that Harley et al. [133] found a decrease in BMI due to prenatal exposure to BPA in girls also indicates that the associations

between BPA and body weight may be complex, especially in regards to developmental exposures. While these studies were strong in terms of methodology and analysis, their inherent limitations due to their cross-sectional nature require further animal and human research, particularly longitudinal studies, in order to elucidate the link between both prenatal and postnatal BPA exposure and obesity.

2.4 Other Health Effects

2.4.1 Thyroid Function

Thyroid function, measured by thyroid hormone concentrations, may be disrupted by BPA in humans. Thyroid stimulating hormone (TSH) is released from the pituitary gland in response to brain signaling, and acts on the thyroid gland to produce thyroxine (T4) and triidothyronine (T3). T3 is also produced in the peripheral organs from the deiodination of T4. The production of thyroid hormones are regulated by negative feedback to the brain [142]. In the Meeker et al. [53] study, higher urinary BPA in males of sub-fertile couples was significantly associated with lower circulating TSH. Meeker and Ferguson [143] found, in an NHANES population, that urinary BPA was inversely related to total T4, and there was some evidence of an inverse relationship with TSH.

Wang et al. [144] studied a cross-sectional population of workers in epoxy resin plants in China, and found that higher total urinary BPA was significantly associated with higher free T3. Although the sample size was small, the magnitude of effect was large, and there was a linear dose-response. Further, in an independent study, Wang et al. [145] studied thyroid function in a previously mentioned population [122]. The sample size was large, and individuals with thyroid

diseases or taking thyroid medications were excluded. They found that higher urinary BPA was significantly associated with higher T3, and also with lower TSH, a finding consistent with other studies. They did not, however, find an association between BPA and T4. Further, the authors found that individuals with increased thyroid function (hyperthyroid and subclinical hyperthyroid) had significantly higher BPA than individuals with normal (euthyroid) and lower thyroid function (hypothyroid and subclinical hypothyroid), indicating higher BPA is associated with increased thyroid function [145].

Again, all these studies were adult, cross-sectional studies, so causal relationships between BPA exposure and thyroid function cannot be confirmed. BPA appears to be elevated in individuals with higher body weight and BMI, and it also appears to be elevated in those with increased thyroid function. Although increased thyroid activity can lead to leaner body weight [146], it is unclear what kind of interactions there are between body weight, thyroid function, and BPA, and if more complex or indirect metabolic mechanisms, possibly involving feedback loops, are involved.

Thyroid function was also studied in newborns, to assess the possibility of disruption during development. Brucker-Davis et al. [101] studied mothers and healthy newborn boys from a prospective study. Maternal serum and milk samples were taken and tested for several xenobiotics, including BPA. There was a slight negative correlation between maternal BPA and TSH in newborns ($p=0.08$), indicating a trend of reduced thyroid function due to BPA exposure during development [101]. A stronger association was found in a more recent study of gestational exposure to BPA in newborns. Chevrier et al. [28] followed mother-child pairs in the

CHAMACOS cohort. Maternal urinary BPA was analyzed at several time points during gestation, and maternal serum thyroid hormone concentrations were also assessed. TSH was measured in the newborns. Higher maternal urinary BPA concentrations were significantly associated with lower maternal T4, when BPA measurements were taken at the time of T4 measurements. Further, maternal BPA was negatively associated with neonatal TSH in boys, but not girls. Among the boys, the association was stronger with BPA measurements taken during the third trimester of gestation, as opposed to the other time points; the authors indicate that this may be a sensitive window of exposure [28]. Because of its longitudinal nature, as well as the adjustment for a wide range of confounders (other chemical exposures, iodine intake during pregnancy), good study design and analytical methodology, this study provides perhaps the strongest evidence of BPA affecting thyroid function in humans.

These human studies indicate that the effects of BPA on thyroid function may be complex, as some hormones seem to be elevated in response to BPA exposure (i.e. T3), and some lowered (i.e. T4 and TSH). It has been shown that BPA and its halogenated derivatives may have both agonistic and antagonistic interactions with the thyroid receptor [9, 147-149], which may explain the complex outcomes reported in the human studies.

2.4.2 Immune Function

General measures of immune function were also shown to be negatively associated with BPA exposure in a strong cross-sectional study of adults and children (ages 6 and older). Clayton et al. [150] examined data from NHANES 2003-2006. They found that urinary BPA was significantly correlated with antibody titers to cytomegalovirus (CMV). Increased CMV antibody titers

indicate a depressed immune system, and can be an early marker of immune dysfunction in humans. In adults (18 and over), higher BPA was associated with increased CMV antibody titer, while in children and adolescents (under 18) higher BPA was associated with decreased CMV antibody titer. The authors suggested that this discrepancy might be due to the duration of exposure to BPA, and that BPA exposure may adversely affect immune function over time [150].

2.4.3 Albuminuria

Albuminuria refers to increased urinary albumin (i.e. an albumin:creatinine ratio of less than 30 mg/g). It is an indicator of endothelial dysfunction in the kidneys, and is a predictor of type-2 diabetes and cardiovascular disease [151, 152]. Two studies have linked total BPA exposure to increased risk of low-grade albuminuria, in both adults and children. Both studies had large sample sizes, good methodology, and large magnitudes of effect. Li et al. [153] found that increased urinary BPA significantly correlated with increased risk of albuminuria in a large cross-sectional population of Chinese adults. Trasande et al. [154] looked at the relationship between BPA and albuminuria in children, in the NHANES 2010-2011 population, and found the same significant association. While the direct health effects of BPA in this instance are unclear, it is known that albuminuria is an indicator of future health problems [155, 156]. The mechanisms of the effects of BPA on the kidney endothelium are not known, but both Li et al. [153] and Trasande et al. [154], suggest that the effects may be caused by BPA-induced oxidative stress within the renal parenchyma.

2.4.4 Oxidative Stress and Inflammation

Tarantino et al. [60] monitored endpoints of chronic inflammation in women with and without PCOS in relation to BPA exposure. Total serum BPA was higher in subjects with increased spleen size, which is an indicator of inflammation. PCOS women with higher BPA concentrations also had increased markers of chronic inflammation: increased hepatic steatosis, higher C-reactive protein (CRP) and interleukin (IL)-6 (trend), and enlarged spleen. As mentioned above, in the women with PCOS, the authors identified 'a different subgroup of PCOS women' with higher BPA exposure and more severe adverse health outcomes (i.e. insulin resistance and signs of chronic inflammation) [60].

Hong et al. [121] examined a large population of Korean adults. There was a suggested positive association ($p < 0.01$) between total urinary BPA and measures of oxidative stress, the reactive oxygen species malondialdehyde (MDA) and 8-hydoxydeoxyguanosine (8-OHdG). However, this was not significant after adjustments [121]. In contrast, Yi et al. [157] found a significant positive correlation between conjugated urinary BPA and MDA (but not 8-OHdG) in Korean women undergoing a clinical trial to measure the effects of wheat grass juice on oxidative stress, however, the sample size of this study was very small.

Lastly, Yang et al. [158], studied men and pre- and postmenopausal women. They found that, in postmenopausal women only, higher total urinary BPA was associated with higher MDA, 8-OHdG, and CRP, suggesting that postmenopausal women may be more sensitive to the effects of BPA than premenopausal women and men [158].

These studies were mostly adult cross-sectional studies which are typically deemed less rigorous than longitudinal studies [36]. However, it may be more biologically relevant to measure exposure at the same time as oxidative stress endpoints, as oxidative stress can be an immediate response to environmental stressors [159]. Further, because BPA exposure in humans is likely continuous [10-12] long-term oxidative stress and inflammation, possibly induced by environmental factors such as BPA, could lead to serious health problems.

2.4.5 Epigenetics, Gene Expression, and Sister Chromatid Exchange

Although it is unclear how changes in the epigenome or gene expression relates directly to adverse health effects in humans, a few studies have found that BPA can change these parameters. Again, although these were all cross-sectional studies, some of these effects may be more immediate than the long-term development of other diseases [160, 161]. Thus, spot samples, which have been shown to be good measures of recent BPA exposure [49], may be better than long-term studies to examine these effects. Hanna et al. [162] studied women from a cross-sectional study involving IVF patients from the population in Bloom et al. [40, 42]. They found that higher unconjugated serum BPA was significantly associated with less methylation at the TSP50_P137 CpG site, specifically, at the TSP50 gene promoter, in whole blood. Although the sample size of this study was small (N=43), the magnitude of effect was large. The TSP50 gene encodes ‘testes-specific protease 50’ which has unknown function. A decrease in methylation indicates increased gene expression at this site. A similar decrease in methylation of this gene is seen in breast cancer tissue [163]. Thus, BPA is associated with altered methylation, but it is unclear what the biological consequences are in this case [162].

In another study by Melzer et al. [164], data from adult men in the InCHIANTI study were examined. They found that higher total urinary BPA was associated with higher expression of two estrogen-responsive genes: ESR2 (ERbeta) and ESRRA (estrogen-related receptor [ERR]alpha). ERRalpha is an orphan receptor, similar in structure to ERalpha, doesn't bind estradiol, and is possibly involved in ligand independent transcriptional activity [165]. These gene changes were measured in blood leukocytes by rtPCR. It is likely that these genes are upregulated to direct estrogenic action of BPA. Again, although these genes are related to estrogenic activation/response, the biological effects are unclear [164].

Lastly, Yang et al. [166] sought to discover any correlation between increased sister chromatid exchange (SCE) and BPA exposure. SCE frequency can be used as a marker of chromosomal stability in response to exposure to a mutagen or carcinogen [167]. In the Yang et al. study, the authors tested conjugated urinary BPA in individuals in a cross-sectional Korean cohort. They found a trend ($p = 0.06$) of a positive correlation between SCE in the lymphocytes and increased urinary BPA [166]. Again, the human health implications of this study are unclear.

3. Discussion and Conclusions

Recent human studies indicate that BPA exposure in adults may be associated with reduced ovarian response and IVF success, reduced fertilization success and embryo quality, implantation failure, miscarriage, premature delivery, reduced male sexual function, reduced sperm quality, altered sex hormone concentrations, PCOS, altered thyroid hormone concentrations, blunted immune function, type-2 diabetes, cardiovascular disease (i.e. heart disease, hypertension, and cholesterol levels), altered liver function, obesity, albuminuria, oxidative stress and

inflammation, and altered epigenetic markers and gene expression. Further, exposure to BPA during gestation could result in increased spontaneous abortion, abnormal gestation time, reduced birth weight, increased male genital abnormalities, and childhood obesity. Particularly strong are the associations between early BPA exposure and altered behavior and disrupted neurodevelopment in children, as well as increased probability of childhood wheeze and asthma. Although an in-depth discussion of potential mechanisms of effects of BPA are beyond the scope of this review, many in vitro studies and in vivo animal studies have supported these proposed adverse health effects due to BPA exposures, at environmentally relevant doses [5, 6, 9, 13, 63, 69, 73, 116, 140, 168-179].

A few studies in this review found no correlation between prenatal BPA exposure and birth weight [91, 96], gestation length [91, 96], infant neurobehavior [104], and male genital abnormalities [58, 100]. Further, no differences were found in two studies looking at childhood BPA exposure and premature puberty [180, 181] and childhood physical development [134]. In adults, some studies found no association between BPA exposure and type-2 diabetes [22, 24, 182], coronary risk [127, 182], and BMI [49, 56, 60, 117, 182] (see Table 1). Additionally, the literature did not support an association between BPA and breast cancer [70, 71] or endometrial disorders [21, 67, 68] when BPA was measured in adulthood.

Six million tons of BPA are produced per year and used in numerous products [144]. Given the sheer number of findings cited above, many in occupational studies, individuals exposed in the workplace need to be protected, and also educated about the possible risks to themselves and their families. Studies that measure the effects in occupationally exposed individuals may be

stronger than those of the general population, as exposure can be better monitored. However, approximately 70% (67) of the human studies found significant adverse effects in non-occupationally exposed populations (Table 1), indicating that low-dose environmental exposure to BPA can cause harmful effects in the global population.

Additionally, several studies focused only on couples being treated for infertility (Table 1). Although this could indicate that adverse effects cannot be generalized to a normal, fertile population, it could also mean that BPA may be linked to infertility, or that there is a population of infertile individuals that are more sensitive to the effects of BPA. Because infertility is on the rise in the Western world [183] it is important to understand adverse reproductive effects, even in a subset of the population. There is also a need for more studies examining the effects of BPA exposure on fertility related endpoints in the general population.

It is extremely important to understand the differences between developmental and adult exposures in the context of these studies. Because of the rapid metabolism and excretion of BPA, which has a half-life of approximately 6 hours in humans [184], spot urine or single serum samples do not necessarily accurately reflect long-term exposure of BPA in individuals. Rather, in all the previously mentioned studies that examined adult populations or cohorts, the serum/urinary BPA samples reflected recent exposures. These samples could therefore accurately be predicting activational effects, such as changes in hormone concentrations and gene expression [19, 51-56, 143, 144, 162, 164]. It has been shown, however, that spot samples reasonably predict long-term exposures in adults [49], so single sample BPA measurements may be accurate measures of more long-term adult exposures in these studies. Therefore, the 'adult'

diseases and outcomes measured in these studies (i.e. IVF success, type-2 diabetes, cardiovascular disorders, etc.) may be due to chronic or long-term activational BPA exposures during adulthood. If these effects are truly activational, then reduction of BPA exposure could cause alleviation of the diseases or disorders.

There is, however, a large body of literature linking prenatal or early environmental exposures to adverse adult outcomes [102]. In the case of prenatal exposure, environmental chemicals can have *organizational* effects on developing systems. Because there are "critical windows of development," in which developing systems are particularly sensitive to hormonal or other disruptions [102], exposure to BPA in utero or early in development could have detrimental and permanent effects later in life. Several of the human studies found associations between maternal BPA exposure during gestation and endpoints in the offspring [10, 20, 28, 87, 92, 94, 103, 105, 114]. In these cases, maternal exposure clearly represents exposures to the developing fetuses [15-17]. Further, in several studies, the timing of maternal exposure to BPA resulted in stronger associations of adverse outcomes of the offspring [28, 103, 114], indicating there may be sensitive windows of time when BPA can adversely affect the developing fetus. There were also several studies that found effects when following-up on postnatal BPA exposures and outcomes in young children [106-109], indicating that the critical windows of BPA exposure may persist postnatally into childhood.

Many of the human studies found associations between BPA exposure and demographic parameters. In the NHANES population, for example, non-Hispanic black individuals had higher BPA exposures than other ethnicities, and Mexican Americans appeared to have the lowest

exposures [117, 124, 129, 150]. However, Mexican American women who lived their entire lives in the US had higher BPA exposures than recent immigrants [28]. Another study found that pregnant African-Americans had significantly higher BPA exposures than Caucasians, with Mexican-American women having intermediate exposures [185]. In the NHANES population, younger individuals tended to have higher BPA exposure [19, 117, 124, 129, 150, 154]. Individuals with lower income and lower education level also tended to have higher BPA exposures [117, 124, 129, 150]. These characteristics were consistent in children as well as adults, when measuring the caregiver's education and income [131]. Smokers also tended to have higher BPA exposures than non-smokers [122]. A higher occupational social class (i.e. higher management positions) was significantly associated with lower BPA exposures [27]. Two studies found higher BPA exposures in men compared to women, possibly having to do with BPA's correlation with higher testosterone [19, 54], although other studies did not find gender differences in BPA exposures [117, 124, 129, 150]. Determining the reason(s) for these demographic differences (i.e. dietary, social, location) is an important focus for future research, in order to understand the sources of exposure and health risks of BPA. For example, Martina et al. [186] studied BPA exposure in a population of Old World Mennonite women, and found their BPA levels to be significantly lower than the NHANES populations, attributing the lower exposure levels to lifestyle factors such as consuming homegrown produce, limited use of personal care products, and limited use of automobiles for transportation.

Certain ethnic populations may be more sensitive to the detrimental effects of BPA. For example, Asian-American women undergoing specific fertility treatments were found to be more sensitive to BPA in terms of oocyte maturation, and Asian-American men had reduced

probability of fertilization with higher BPA exposure [41]. Additionally, it has been suggested that Korean adults may not be sensitive to the effects of BPA in terms of type-2 diabetes [22]. Further research is needed to establish if certain populations (i.e. ethnic, demographic, physiological status) may be more sensitive to the effects of BPA exposure than others.

While these studies largely adjusted for factors such as age, BMI, smoking, socio-economic status, ethnicity, and other parameters, one potential confound is the possibility that other hormonally active environmental compounds may be responsible for the health effects documented, or that other compounds may blunt adverse health outcomes or act synergistically with BPA. Many of the studies reviewed also measured exposure to other compounds that may cause disruptive effects [20, 23, 25, 28, 32, 45-47, 52, 67, 96, 101, 117, 121, 127, 128, 131, 143, 150, 154, 162, 180]. Statistically adjusting for the presence of these chemicals did not change the outcomes, strengthening the likelihood that the effects documented were specifically due to BPA exposure.

A further confound that could possibly affect these outcomes is that diseases such as obesity, type-2 diabetes, and cardiovascular disease could be a product of consumption of a larger amount of packaged food and higher caloric intake, and thus these individuals may be exposed to higher concentrations of BPA through food packaging or other lifestyle factors. It is unclear if eating a higher amount of canned food alone can contribute to these diseases, but because of the ubiquitous nature of BPA in food packaging, it would be almost impossible to carry out a long-term study of the influence of canned food itself on human health. Although it is difficult to tease out such related factors, BMI was adjusted for as a confound in the NHANES studies, which still

showed strong associations between BPA exposures and disease [27, 118-120, 124]. Further, Trasande et al. [131] found an inverse relationship between caloric intake and BMI in their study, indicating the obese individuals were possibly exposed to less BPA, rather than more. Lastly, even though consumption of packaged food may contribute to nutritional deficits, it is also highly likely that food packaging materials could also leach BPA and other harmful EDCs [187].

It is also important to understand the differences in methodologies that can affect outcomes in these studies. BPA can be measured in serum as well as urine. While urinary BPA testing is less invasive, it measures the BPA excreted, not necessarily the current in vivo exposures. Thus, serum BPA may be a better measure of exposure [2]. However, due to the continuous exposure through the diet [188], urinary BPA has been generally accepted as a good measure of recent exposure [49]. When measuring BPA in urine, however, variations in the dilution can alter the results. Thus, the urine BPA must be normalized to specific gravity (SG) or per grams creatinine. Although many of the studies reported non-adjusted values (Table 1), they were largely normalized when performing statistical analysis. For example, the NHANES studies were normalized to creatinine [27, 118, 119, 124, 129, 130, 143, 150, 189]. However, some researchers opt to normalize using SG over creatinine, stating that creatinine concentrations can possibly be confounded by physiological factors (muscle mass, physical activity, etc.) or the route of metabolism of BPA [39]. Additionally, because spot urine sampling may provide limited information, daily excretion rates can be determined by 24-hour urine collections [19]. If spot urine samples are collected, the time of day of collection should be consistent, or at least adjusted for, as it has been shown that urinary BPA concentrations are variable depending on the time of

collection [12, 49, 53]. Further, individuals with reduced renal function (measured by estimated glomerular filtration rate) had reduced urinary excretion of BPA, indicating the physiological state of the individual could have an effect on excretion rates [190].

Serum or urinary BPA is most commonly measured using high performance liquid chromatography (HPLC) or HPLC-tandem mass spectrometry (LC-MS/MS). Other studies utilize an enzyme-linked immunosorbent assay (ELISA) or radioimmunoassay (RIA) to determine total BPA in the urine or serum [54-56, 58, 87, 101]. The ELISA and the RIA have been found to positively correlate with HPLC measurements [191, 192], although others have found ELISAs to be less sensitive than HPLC [193]. Another factor to consider is the type of BPA measured (i.e. total, unconjugated or conjugated). Total BPA contains both the unconjugated and the biologically inactive conjugated fractions [194]. Thus, measurement solely of unconjugated BPA may more accurately reflect the biological activity [40-42] but only a few of the human studies measured unconjugated serum BPA as the sole biomarker for BPA exposure [40-42, 58, 162]. This measurement may be less relevant for urinary BPA, as most of the BPA excreted in the urine is the conjugated form [194]. In fact, a few of the studies used only urinary conjugated BPA as a biomarker of exposure [70, 157, 166]. An important area of future research would be to develop a scientifically sound, consistent, established protocol for measuring BPA exposure in humans in order to better carry out inter-study comparisons.

The analytical methods employed can also change the results of a study, even with the same data set. For example, LaKind et al. [182] repeated previous studies using the NHANES population data [117, 118, 120], examining the relationship between cardiovascular disease and type-2

diabetes, and urinary BPA. They found no relationship between CHD, heart attack, and type-2 diabetes and urinary BPA, contrary to the previous studies using these data [182]. The previous studies limited their analysis to certain ages (18-74, or over 20) and used physician-diagnosed endpoints, as well as HbA1c measurements for type-2 diabetes diagnosis [117, 118, 120]. LaKind et al. [182] analyzed all ages, used glucose levels to diagnose type-2 diabetes, and included other covariates (such as cholesterol level and hypertension). LaKind et al. [182] therefore concluded that the NHANES data might not be appropriate for studying the long-term effects of BPA on diseases. However, it is important to note that the exclusion criteria and endpoints used in the previous studies were biologically based, and for good reason. For example, children were presumably excluded from the analysis in order to examine adult disease only, without the confound of developmental influences. Further, as suggested in other studies, glucose measurement may not be the most accurate measure of incidence of type-2 diabetes, as medication can alter glucose levels [24]. Thus, physician-diagnosed diabetes or other biological endpoints (such as HbAc1) may be more precise. Finally, LaKind et al. [182] included in their analyses covariates that may also be altered by BPA exposure, such as hypertension [123] and cholesterol level [127], which may have contributed to their non-significant findings. It is clear that endpoint choice and statistical methodology are important factors in study outcomes, and the biological significance of the analyses and endpoints used need to be carefully considered and reported.

Several of the studies showed NMDRCs [25, 48, 95, 131]. The concept of non-monotonic responses is not new—vitamin toxicity is a well-known example [195]. Further, these studies examined non-occupationally exposed populations, and thus low, environmentally relevant,

exposures [25, 48, 95, 131]. Although, controversy has arisen about NMDRC and the 'low-dose hypothesis' in regards to EDC action [196], there is increasing evidence that environmentally relevant exposures to EDCs can cause significant effects [2]. Because the endocrine system shows clear non-monotonic actions [2], it is not surprising that some of the effects seen in humans followed a NMDRC. The endocrine system is exquisitely sensitive to low doses of hormone due to receptor kinetics, tissue specificity, receptor specificity, nuclear vs. membrane receptor effects, etc. When concentrations of endocrine active substances exceed the physiological amounts (as is often the case in 'traditional' toxicology studies) these sensitive endocrine effects can be attenuated [2]. Thus, incorporating these epidemiological studies, which examine the health effects in environmentally exposed humans, can help elucidate these low-dose, non-monotonic effects.

In the United States and Europe, regulating bodies have determined that 50 μg/kg/day of BPA exposure is the current tolerable daily intake (TDI) for humans, based largely on rodent multigenerational, subchronic, oral toxicity studies, measuring endpoints such as body weight and developmental malformations. Although low doses were tested, more sensitive endocrine disruptive endpoints were not examined when determining the TDI for BPA [164, 197-199]. Because endocrine disruptors often follow non-monotonic dose-response curves and can exhibit greater effects at lower doses [2], and because of the numerous laboratory studies indicating lower doses cause adverse effects [2, 5], researchers have raised concerns that the current 'safe' cutoff for BPA is much too high [200]. Li et al. [23] reported the mean urinary BPA concentration in the occupationally exposed men was 38.7 μg/L. According to them, the urinary output of BPA from the TDI of 50 μg/kg/day is calculated to be 2,678.5 μg/L/day. Although

these men were workers in BPA and epoxy resin processing plants, they were still exposed to BPA concentrations ~70 times below the TDI, and yet had adverse reproductive effects [23]. Wang et al. [132] estimated BPA intake of 8.22 ng/kg/day of the children in their study. These children had adverse health effects, with a much lower BPA exposure than the TDI [132]. Melzer et al. [164] also estimated the mean excretion of BPA in their study to be 5.84 μg/day, lower than that of the TDI. The NHANES population (2003-2006) had an estimated median daily intake of 0.034 μg/kg/day, with significant adverse effects associated with thyroid function, obesity, diabetes, cardiovascular disease, liver function, and immune function [27, 118, 119, 124, 129, 130, 143, 150]. The urinary/serum BPA concentrations found in the current human studies ranged from 0.4 to 9 μg/L (Table 1), much lower than the TDI excretion rate of 2,678.5 μg/L/day. The fact that there are significant adverse effects in populations exposed to BPA at concentrations ~70 to 5000 times lower than the TDI (Table 1), indicates that the safe exposure to BPA may be much lower than previously thought in humans.

There has been a rapid increase in the number of peer-reviewed studies linking BPA exposure to adverse health outcomes in the last several years. These studies suggest that BPA exposure may have significant implications for human health and fertility, especially during development, and in sensitive populations. Government regulators are beginning to respond—the Food and Drug Administration (FDA) called BPA a 'chemical of concern' and recently (July 2012) banned its use in baby bottles and sippy cups [201], however, the margin of safety has not been lowered below 50 μg/kg/day. Although it is imperative that more longitudinal/prospective-type studies are done with increased sample sizes and in a variety of human populations to create a stronger link between BPA exposure and human health outcomes, these studies will take many years and

require considerable resources. The current literature-to-date indicate BPA in the environment may pose a health risk to humans. Further, it has been recommended that the regulation of BPA should be revisited [200], in order to protect human health.

4. Acknowledgements

This work was funded by The Arkansas Community Foundation, The Winslow Foundation, and The Johnson Family Foundation. The author would like to thank Carol Kwiatkowski, Ashley Bolden, John Vandenbergh, and Theo Colborn for their critical review of this manuscript.

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Categories	Study	Study Type[#]	N	Population Type[§]	BPA Conc.[+]	Results
Major Category: Reproduction						
Fertility	Mok-Lin et al. 2010 [39]	Prosp. cohort	84	Women undergoing IVF treatment aged 18-45. [MGH]	2.6[a]	Higher BPA associated with poorer
Fertility	Ehrlich et al. 2012 [38]	Prosp. cohort	174	Women undergoing IVF treatment aged 18-45. [MGH]	2.3[a]	Higher BPA associated with poorer number of mature oocytes, and redu oocytes.
Fertility	Bloom et al. 2011 [40]	Prosp. cohort	44	Women undergoing IVF treatment aged 31-39. [UCSF]	2.5[b]	Higher BPA associated with lower hyperstimulation with hCG.
Fertility	Fujimoto et al. 2011 [41]	Prosp. cohort	83	Men and women from couples undergoing IVF treatment. [UCSF]	0.3-2.5[m,b]	Decrease in the probability for fertil in women and Asian men. Increased resulted in a lower probability of ma
Fertility	Bloom et al. 2011 [42]	Prosp. cohort	54	Men and women from couples undergoing IVF treatment. [UCSF]	0.5-3.3[m,b]	Higher serum BPA associated with but not female, partners.
Fertility[ns]	Chen 2013 [43]	Case-control	1590	Idiopathic infertile men and controls in China.	0.6[d]	Urinary BPA was not associated wi
Fertility	Ehrlich et al. 2012 [44]	Prosp. cohort	137	Women undergoing IVF treatment aged 18-45. [MGH]	2.6[a]	Higher urinary BPA associated with failure.
Fertility	Caserta et al. 2013 [45]	Case-cont.	61	Infertile women and fertile controls aged 18-40.	n/a	Serum BPA was detected in signific in controls.
Male Sexual Function	Li et al. 2010 [47]	Occ. cohort	550	Men working in BPA and epoxy resin plants and non-exposed controls. [LI]	1.2-57.9[m,c]	Occupationally exposed workers ha sexual function than controls, in a d
Male Sexual Function	Li et al. 2010 [46]	Occ. cohort	427	Men working in BPA and epoxy resin plants and non-exposed controls. [LI]	1.2-53.7[m,c]	Higher urinary BPA was significant reported sexual function.
Sperm Quality	Li et al. 2011 [23]	Occ. cohort	218	Men working in BPA and epoxy resin plants and non-exposed controls. [LI]	1.4-38.7[m,c]	Higher urinary BPA was significant quality measures.
Sperm Quality	Meeker et al. 2010 [48]	Cross-sec.	190	Male partners of couples seeking treatment at a fertility clinic. [MGH]	1.4[d]	There was significant correlation of sperm count, sperm morphology, sp

Sperm Quality	Xiao et al. 2009* [33]	Cross-sec.	36	BPA exposed and control workers in China.	0.0-102.0[m,b]	Serum BPA was higher in exposed exposed workers had significantly l normal sperm' than controls.
Sex Hormones Concentrations	Hanaoka et al. 2002 [52]	Cross-sec.	84	Workers exposed occupationally to BADGE and controls.	1.0-2.1[m,c]	The workers exposed to BADGE ha BPA than controls, and significantly
Sex Hormone Concentrations/PCOS	Takeuchi & Tsutsumi 2002 [54]	Case-cont.	41	Healthy women, healthy men, and PCOS women	0.6-1.5[b]	Serum BPA, as well as T and FT we men, compared to healthy women.
Sex Hormone Concentrations/PCOS/ Obesity	Takeuchi et al. 2004 [55]	Case-cont.	73	Women with and without PCOS, with lean and obese subgroups, and women with hyperprolactinemia or hypothalamic amenorrhea.	0.7-1.2[b]	In all subjects, increased serum BPA total T, FT androstendione, and DH obese women had higher BPA than PCOS women (both obese and non- concentrations than non-obese contr
Sex Hormone Concentrations/Sperm Quality	Mendiola et al. 2010 [51]	Cross-sec.	375	Fertile men.	1.5[d]	Increased urinary BPA was signific FAI, FT, and seminal volume, and w
Sex Hormone Concentrations/Obesity	Galloway et al. 2010 [19]	Cross-sec.	715	Italian adults.[INCHIANTI]	3.6[c]	Higher urinary BPA was associated women. In premenopausal women, increased SHBG. Urinary BPA was size.
Sex Hormone Concentrations/Thyroid Function	Meeker et al. 2010 [53]	Cross-sec.	167	Male partners of couples seeking treatment at a fertility clinic.[MGH]	1.3[a]	Higher urinary BPA was associated B, higher FSH:inhibin B ratio, and l also associated with lower TSH con
Sex Hormone Concentrations	Hao et al.* 2011 [31]	Occ. case-cont.	155	Women workers occupationally exposed to BPA and controls.	n/a	Prolactin concentrations were signif women vs. non-exposed. Further, pr exposed to BPA for longer than 5 y
Sex Hormone Concentrations/PCOS/ Diabetes	Kandaraki et al. 2011 [56]	Cross-sec.	171	Women with and without PCOS, with lean and obese subgroups.	0.7-1.1[b]	Serum BPA was significantly highe women (both in the control and PC significant positive association betw concentration. BPA was positively c
Sex Hormone Concentrations	Tang et al. 2012 [59]	Cohort	154	Children ages 8-13 who were born and lived in polluted and control river areas.	n/a	Children from polluted river areas (and other chemicals in the drinking had significantly lower serum E2 ar
Endometrial Disorders	Cobellis et al. 2009 [67]	Case-cont.	69	Women with endometriosis and controls, aged 18-44.	2.9[b]	BPA was significantly more likely t women with endometriosis, compar
Endometrial Disorders	Hiroi et al. 2004 [68]	Cross-sec.	37	Women with endometrial hyperplasia (EH), endometrial cancer, and controls.	1.4-2.9[b]	Serum BPA was significantly lower simple EH patients. Endometrial ca BPA than simple EH patients and c

				controls.		
Endometrial Disorders[ns]	Itoh et al. 2007 [21]	Cross-sec.	140	Infertile women aged 20-45.	0.8-1.6[c]	There was a trend for higher urinary severe endometriosis (p=0.08), and creatinine.
PCOS/Inflammation/ Type-2 Diabetes	Tarantino et al. 2012 [60]	Cross-sec.	60	Lean and obese women with PCOS and controls, aged ~23-33.	0.1-0.7[b]	Women with PCOS had significantl associated with increased spleen siz serum BPA had more severe insulin increased markers of chronic inflam
Breast Cancer[ns]	Yang et al. 2009 [70]	Case-cont.	152	Women with breast cancer and controls.	1.7[b]	There was a non-significant elevatio There were some significant associa cancer risks.
Breast Cancer[ns]	Aschengrau et al. 1998 [71]	Case-cont.	1014	Women with breast cancer and controls, surveyed for occupational exposures.	n/a	BPA exposure was not associated w
Miscarriage	Sugiura-Ogasawara et al. 2005 [87]	Case-cont.	77	Women with recurrent miscarriages, and healthy controls, aged 26-36.	0.8-2.6[b]	Serum BPA of women who had rec significantly higher than healthy co
Miscarriage	Zheng et al.* 2012 [30]	Case-cont.	170	Women with recurrent miscarriage and controls.	4.0-9.0[b]	Women who had recurrent miscarri BPA than controls, in a dose-depen
Premature Delivery	Cantonwine et al. 2010 [20]	Case-cont.	60	Mexican pregnant women.	1.5[a]	There was a significant relationship weeks) with elevated BPA.
Major Category: Development						
Birth Weight	Miao et al. 2011 [92]	Occ. cohort	587	Children from mothers or fathers exposed occupationally to BPA, or not exposed. [LI]	n/a	Children with exposed mothers had than children of unexposed mothers response relationship.
Birth Weight/Fetal Growth	Philippat et al. 2012 [25]	Case-cont.	287	French mother-child cohort.	0.4-10.1[d]	Trend of an inverse U-shaped assoc BPA exposure. Higher urinary BPA circumference.
Birth Weight/Fetal Growth	Chou et al. 2011 [95]	Prosp. cohort	97	Taiwanese mother-infant pairs.	0.5-2.5[b]	Higher serum BPA was significantl weight and smaller size for gestatio female infants.
Birth Weight/Gestational Length[ns]	Padmanabhan et al. 2008 [91]	Cross-sec.	40	Pregnant mothers.	5.9[b]	No significant associations between length and birth weight of newborns

Birth Weight/BMI	Wolff et al. 2008 [96]	Birth cohort	404	Mother-infant pairs.	0.4-35.2[d]	No significant associations between weight. There was a positive correla maternal BMI in BPA.
Male Genital Abnormalities	Miao et al. 2011 [94]	Occ. cohort	153	Sons from mothers or fathers exposed occupationally to BPA, or not exposed. [LI]	n/a	Boys from exposed parents had sho manner.
Male Genital Abnormalities/Sex Hormone Concentrations	Fénichel et al. 2012 [58]	Prosp. cohort	152	Newborn boys born with or without cryptorchidism.[BD]	1.1-1.3[b]	There was no difference between co control and cryptorchid boys. There correlation between cord blood BPA inhibin.
Male Genital Abnormalities[ns]	Chevrier et al. 2012 [100]	Nested case-cont.	275	Mothers and newborn boys born with cryptorchidism, hypospadias, and controls.	0.4-25.7[d]	There was no relationship between pregnancy and hypospadias or cryp
Neurobehavioral Development	Braun et al. 2009 [103]	Prosp. cohort	249	Pregnant women and offspring at 2 years of age.[HOMES]	1.3-1.8 [m,d]	Higher urinary BPA was associated behaviors in girls but not boys.
Neurobehavioral Development	Braun et al. 2011 [10]	Prosp. cohort	244	Pregnant women and offspring at 3 years of age. [HOMES]	2.0-4.1 [m,d]	Increased maternal urinary BPA wa and depressed behavior and poorer
Neurobehavioral Development	Perera et al. 2012 [105]	Prosp. cohort	198	African-American and Dominican-American mother-child cohorts. [CCCEH]	2.0-3.9[a]	Higher maternal urinary BPA was s problematic scores in Emotionally I in boys. In girls, maternal BPA was scores, with significance in Anxious Behavior.
Neurobehavioral Development	Bellinger et al. 2007 [106]	Random. clinical trial	534	Children with amalgam or composite fillings (containing BPA) aged 6-10.[NECAT]	n/a	There was a significant reduction in children with composite fillings.
Neurobehavioral Development	Bellinger et al. 2008 [107]	Random. clinical trial	395	Children with amalgam or composite fillings (containing BPA) aged 6-10. [NECAT]	n/a	The children with composite treatm scores overall, with poorer scores in problem behaviors, activities, and d
Neurobehavioral Development	Maserejian et al. 2012 [108]	Random. clinical trial	434	Children with amalgam or composite fillings (containing BPA) aged 6-10. [NECAT]	n/a	In children with composite fillings, scores in Letter Fluency and color n scores in some measures of executiv
Neurobehavioral Development	Maserejian et al. 2012 [109]	Random. clinical trial	434	Children with amalgam or composite fillings (with and without BPA) aged 6-10. [NECAT]	n/a	Children with bisGMA-based comp increased anxiety, depression, socia problems.
Neurobehavioral Development	Miodovnik et al. 2011 [112]	Prosp. cohort	137	Mother-child cohort.	1.2[d]	There was a significant association BPA and autistic behaviors in adjus

Development	al. 2011 [112]	cohort				BPA and autistic behaviors in adjus
Neurobehavioral Development[ns]	Yolton et al. 2011 [104]	Prosp. cohort	350	Mother-infant pairs.[HOMES]	1.7-1.8[d]	The was no correlation between ma neurobehavioral abnormalities
Child Wheeze	Spanier et al. 2012 [114]	Prosp. birth cohort	365	Mother-infant pairs.[HOMES]	2.4[c]	Higher maternal urinary BPA was a wheeze in the child at 6 months of a diminished by 3 years of age.
Child Asthma	Donohue et al. 2013 [115]	Prosp. birth cohort	568	African-American and Dominican-American mother-child cohorts.[CCCEH]	1.8-3.8[d]	Urinary BPA measured in 3 year ol wheeze at 5 and 6 years. Urinary BI positively associated with wheeze a and 7 years was associated with astl maternal urinary BPA was associate asthma in 5-year-old offspring.
Premature Puberty[ns]	Wolff et al. 2008 [180]	Cross-sec.	192	9-year old girls.[BCERC]	0.1-0.2[c]	Urinary BPA was not associated wi
Premature Puberty[ns]	Wolff et al. 2010 [181]	Prosp. cohort	1151	Girls aged 6-8, followed through puberty.[BCERC]	2.0[d]	There was no association between u hair development.
Premature Puberty	Qiao et al. 2010* [32]	Nested Case-cont.	210	Girls with precocious puberty and controls.	n/a	Serum BPA was significantly eleva puberty compared to controls. High associated with increased uterine an
Major Category: Metabolic Disease						
Type-2 Diabetes/ Cardiovascular Disease/Liver Function/Obesity	Lang et al. 2008 [117]	Cross-sec.	1455	NHANES: 2003-2004, Adults aged 18-74.	4.5-4.7[d]	Higher urinary BPA was significant diagnosis of cardiovascular disease, concentrations of some liver enzym
Type-2 Diabetes	Shankar & Teppala 2011 [119]	Cross-sec.	3967	NHANES: 2003-2008, Adults older than 20.	3.9-4.0[d]	Higher urinary BPA was significant 2 diabetes.
Type-2 Diabetes[ns]	Ning et al. 2011 [24]	Cross-sec.	3423	Adults from Shanghai aged 40 or older.[SC]	0.8[d]	Higher urinary BPA was weakly ass diabetes as measured by blood gluc
Type-2 Diabetes[ns]	Kim & Park 2012 [22]	Cross-sec.	1210	Korean adults older than 40.	2.1[d]	Higher urinary BPA was weakly ass of diabetes. Several demographic fa for significant associations between
Type-2 Diabetes/ Cardiovascular Disease/Liver Function	Melzer et al. 2010 [118]	Cross-sec.	2948	NHANES: 2003-2004 and 2005-2006.	1.8-2.5[d]	Higher urinary BPA was significant cardiovascular disease, and liver en fewer associations in 2005-2006.

Disease/Liver Function						
Type-2 Diabetes	Silver et al. 2011 [120]	Cross-sec.	4389	NHANES: 2003-2008, aged 20 or older.	2.0[d]	Higher urinary BPA was significant incidence of type-2 diabetes and he
Cardiovascular Disease	Melzer et al. 2012 [126]	Cross-sec.	591	Individuals with coronary artery disease (CAD), and normal coronary arteries.[MAGICAD]	1.3-1.5[m,d]	Individuals with severe and interme higher urinary BPA compared to co
Cardiovascular Disease	Melzer et al. 2012 [27]	Nested Case-cont.	1619	Individuals with CAD and controls aged 40-74.[MAGICAD]	1.2-1.4[d]	Higher early urinary BPA was posit incident CAD during 10.8 years of
Cardiovascular Disease	Shankar et al. 2012 [124]	Cross-sec.	745	NHANES: 2003-2004, Adults 40 years and older.	2.3[d]	Higher urinary BPA was significant prevalence of peripheral arterial dis
Cardiovascular Disease	Shankar & Teppala 2012 [123]	Cross-sec.	1380	NHANES: 2003-2004, Adults older than 20.	n/a	Higher urinary BPA was associated hypertension.
Cardiovascular Disease	Bae et al. 2012 [125]	Cross-sec.	521	Korean adults, aged 60 and over.	1.2[c]	Higher urinary BPA was associated and increased hypertention.
Cardiovascular Disease	Olsén et al. 2012 [127]	Cross-sec.	1016	Swedish adults aged 70.	n/a	Higher serum BPA associated with cholesterol. Other factors of corona associated with BPA.
Cardiovascular Disease/Type-2 Diabetes[ns]	LaKind et al. 2012 [182]	Cross-sec.	4842	NHANES: 2003-2010.	n/a	Urinary BPA was not significantly disease, heart attack, or type-2 diab
Obesity	Carwile & Michels 2011 [129]	Cross-sec.	2747	NHANES: 2003-2006, Individuals ages 18-74.	2.1[c]	Higher urinary BPA was significant and waist circumference.
Obesity	Wolff et al. 2007 [128]	Cross-sec.	90	Girls aged 6-8, followed through puberty.[BCERC]	2.0[d]	Girls in the 85th or higher percentil urinary BPA.
Obesity/Type-2 Diabetes	Wang et al. 2012 [122]	Cross-sec.	3390	Adults in Shanghai aged 40 or older.[SC]	0.8[d]	Higher urinary BPA was significant abdominal obesity, and insulin resis
Obesity	Wang et al. 2012 [132]	Cross-sec.	259	School children in Shanghai, ages 8-15.	0.4[a]	Higher urinary BPA was significant
Obesity/Sex Hormone Concentrations	Zhao et al. 2012 [57]	Cross-sec.	282	Healthy premenopausal, non-obese women from Shanghai, ages 20-55.	2.3[d]	Urinary BPA was significantly posi weight, BMI, fat mass, and serum l association between BPA and E2.
Obesity	Trasande et al. 2012 [131]	Cross-sec.	2838	NHANES: 2003-2004, Children ages 6-19.	2.8[d]	Higher urinary BPA was associated

	al. 2012 [131]	sec.		Children ages 6-19.		
Obesity	Shankar et al. 2012 [130]	Cross-sec.	3967	NHANES: 2003-2008, Adults older than 20.	3.9-4.0[d]	Higher urinary BPA was strongly as waist circumference.
Obesity	Harley et al. 2013 [133]	Long. birth cohort	402	Mother-9-year-old child pairs.[CHAMACOS]	1.0-2.3[d]	Higher maternal urinary BPA was a body fat and odds of overweight/ob urinary BPA, measured at 9 years, v BMI, percent body fat, and odds of
Obesity[ns]	Mahalingaiah et al. 2008 [49]	Cross-sec.	82	Men and women seeking infertility treatment.	1.3[d]	Urinary BPA was not associated wi
Obesity/Growth and Development[ns]	Maserejian et al. 2012 [134]	Random. clinical trial	474	Children with amalgam or composite fillings (containing BPA) aged 6-10. [NECAT]	n/a	No significant differences between fat, or growth rate.
Major Category: Other						
Thyroid Function/Male Genital Abnormalities[ns]	Brucker-Davis et al. 2011 [101]	Prosp. cohort	164	Newborn boys born with or without cryptorchidism.[BD]	0.9[m,b]	Weak trend for a negative correlatio was no association between BPA an
Thyroid Function	Chevrier et al. 2013 [28]	Long. birth cohort	364	Mother-child pairs.[CHAMACOS]	1.1-1.2[c]	Maternal urinary BPA concentration associated with maternal T4. Matern with neonatal TSH in boys.
Thyroid Function	Wang et al. 2012 [144]	Cross-sec.	28	Workers in epoxy resin plants in China.	32.0[c]	Higher urinary BPA was significant
Thyroid Function	Meeker & Ferguson 2011 [143]	Cross-sec.	1675	NHANES Study: Adults.	n/a	Higher urinary BPA was inversely r
Thyroid Function	Wang et al. 2013 [145]	Cross-sec.	3394	Adults in Shanghai aged 40 or older.[SC]	0.81[d]	Higher urinary BPA was significant lower TSH.
Immune Function	Clayton et al. 2011 [150]	Cross-sec.	2920	NHANES: 2003-2006, Adults and children aged 6-49.	4.4[d]	Urinary BPA was positively associa adults (18 and over), and negatively
Albuminuria	Li et al. 2012 [153]	Cross-sec.	3055	Chinese adults, aged 40 or older.[SC]	0.8[d]	Higher urinary BPA was associated albuminuria in adults.
Albuminuria	Trasande et al. 2013 [154]	Cross-sec.	710	NHANES: 2009-2010, Children ages 6-19.	1.9[d]	Higher urinary BPA was associated albuminuria in children.

Oxidative Stress and Inflammation/Type-2 Diabetes	Hong et al. 2009 [121]	Cross-sec.	960	Korean adults aged ~40-60.	2.7[d]	There was a non-significant associa measures of oxidative stress. There between increased insulin resistance
Oxidative Stress and Inflammation	Yi et al. 2011 [157]	Clinical trial	14	Korean women.	1.8[c]	Higher urinary BPA was associated stress biomarkers.
Oxidative Stress and Inflammation	Yang et al. 2009 [158]	Cross-sec.	485	Men, pre- and postmenopausal women aged ~40-64.	0.6[c]	In postmenopausal women only, hig with increased oxidative stress and
Epigenetics	Hanna et al. 2012 [162]	Cross-sec.	43	Women undergoing IVF treatment aged 31-39.[UCSF]	2.4[b]	Higher serum BPA was significantl at the TSP50 gene promoter.
Gene Expression	Melzer et al. 2011 [164]	Cross-sec.	96	Italian men aged 20-76.[INCHIANTI]	3.7[d]	Higher urinary BPA is associated w estrogen-responsive genes: ESR2 (E in peripheral blood leukocytes.
Sister Chromatid Exchange[ns]	Yang et al. 2006 [166]	Cross-sec.	172	Korean adults.	7.9[m,d]	Higher urinary BPA had a weak pos lymphocytes.

*, In Chinese, abstract only was reviewed.

[§], Studies using the same or part of the same cohort, cross-sectional population, or clinical trial are indicated with a superscript abbreviation: MGH, Massachusetts General Hospital; UCSF, University of California, San Francisco; LI, Li et al. Chinese occupational studies; INCHIANTI, Cross-sectional population from Chianti, Italy; BD, Brucker-Davis et al. population, infants with cryptorchidism; HOMES, The Health Outcomes and Measures of the Environment Study; CCCEH, The Columbia Center for Children's Environmental Health; CHAMACOS, The Center for the Health Assessment of Mothers and Children of Salinas; NECAT, The New England Children's Amalgam Trial; BCERC, Breast Cancer and the Environment Research Center; SC, cross-sectional population from Songnan Community, China; MAGICAD, The Metabolomics and Genomics in Coronary Artery Disease Study. Studies using NHANES data are indicated.

[+], Mean or geometric mean BPA of participants, unless otherwise noted. Ranges of BPA indicate several reported means/medians (i.e. for different groups) or a reported range.

[a], μg/L, urinary BPA adjusted for specific gravity (SG).

[b], μg/L, serum BPA.

[c], μg/g, urinary BPA adjusted for creatinine (Cr).

[d], μg/L, unadjusted urinary BPA.

[m], median.

[#], Prospective cohort, occupational cohort, cross-sectional study, case-control study, occupational case-control study, birth cohort, nested case-control study, case report, randomized clinical trial, longitudinal birth cohort.

[ns], No significant effects found in the study.

n/a, Not applicable or not reported.