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**Is Bisphenol A an environmental obesogen?**

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**ABSTRACT**

Bisphenol a (BPA) is an endocrine disruptor with an estrogenic activity that is widely produced for the manufacture of polycarbonate plastic, epoxy resin and thermal paper. Its ubiquitous presence in the environment contributes to broad and continuous human exposure which has been associated with deleterious health effects. Despite numerous controversial discussions and a lack of consensus about BPA's safety, growing evidence indicates that BPA exposure positively correlates with an increased risk of developing obesity. An updated analysis of the epidemiological, *in vivo* and *in vitro* studies indicates that BPA should be considered an obesogenic environmental compound. Precisely, BPA exposure during all life stages correlates with increased body weight and/or body mass index (BMI). Developmental periods that include prenatal, infancy and childhood appear to be critical windows with increased sensitivity to BPA effects. Finally, blood analysis and *in vitro* data clearly demonstrate that BPA promotes adipogenesis, lipid and glucose dysregulation and adipose tissue inflammation, thus contributing to the pathophysiology of obesity. Future prevention efforts should now be employed to avoid BPA exposure and more research to determine in depth the critical time windows, doses and impact of long-term exposure of BPA is warranted in order to clarify its risk assessment.

## INTRODUCTION

Although 600 million people are currently facing energy deficits exposing them to undernutrition, 1.9 billion people worldwide are overweight, with 600 million of those classified as obese [1]. The growing rate of overweight and obese individuals clearly characterizes the current worldwide “nutrition paradox”. Whereas undernutrition has declined since 2007, obesity is now considered an epidemic and affects both adults and children [1]. An increase in caloric intake and a decrease of energy expenditure are the main risk factors for developing obesity. However, this energy imbalance, as well as genetic predispositions, do not seem to be fully responsible for the epidemiological rise of obesity worldwide [2]. Growing evidence strongly suggests that environmental chemicals, and particularly endocrine disruptors (EDs), are an additional risk factor explaining the global obesity epidemic [3–5]. The term “endocrine disruptor” was first mentioned in the 1990s and is historically associated with the field of developmental organs, reproductive toxicology and wildlife biology [6]. An ED is precisely defined as a substance or an exogenous mixture that is able to interfere with the endocrine system and consequently cause adverse effects in a healthy organism, its progeny, or other subpopulations [7]. Through the secretion of adipokines, adipose tissue is considered an endocrine organ and can be targeted by EDs, thus potentially leading to adipose tissue dysfunction and inflammation. These biological disorders appear during the pathophysiology of obesity and confirm the causative link between ED exposure and the “obesogen hypothesis” [3,8–10]. Obesogens are defined as chemicals that inappropriately alter metabolic functions such as lipid homeostasis and fat storage, energy balance, regulation of appetite and satiety in order to increase fat accumulation and, eventually, lead to the development of obesity [11–13]. Bisphenol a (BPA) was one of the first compounds identified as an obesogen alongside pesticides, heavy metals, polychlorinated bisphenyls (PCBs) [3,5,14]. BPA is a plastic and thermal paper component ubiquitously present in the environment and possesses estrogenic activity. Numerous controversial discussions concerning the impact of BPA exposure on human health are still debated despite emerging data demonstrating that BPA is associated with infertility, cancer and metabolic disorders like obesity [8,9].

The aim of this review is to provide an updated analysis of the literature focusing on the association between BPA exposure and the development of obesity.

## OBESOGENIC ACTIVITY OF BISPHENOL A

### 1 – BPA

BPA (4,4'-isopropylidenediphenol or 2,2'-bis(4-hydroxyphenyl)-propane, CAS 80-05-7) is a white crystalline compound with a molecular weight of 228.29 g/mol, a melting-point of 156 °C and a water-octanol partition coefficient (logP) of 3.32, and is relatively soluble in lipophilic phases with low solubility in water (Figure 1) [15].

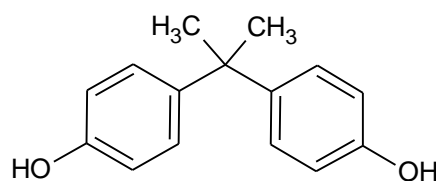


Figure 1: Molecular structure of BPA

BPA is one of the most widely produced compounds worldwide for the manufacture of polycarbonate plastic and epoxy resin with an estimated annual production that reached 6.8 million tons in 2013 [16]. BPA is found in pipes, food containers, bottles, toys, soaps, lotions, shampoo, nail polish, sunscreen, electronic equipment, car equipment, car tires, flame, retardants and more [17,18]. It is also used for its stabilizing and antioxidant properties and in thermal and carbonless paper manufacturing [19].

In 2010, after growing evidence suggested an association between BPA exposure and deleterious effects for human health, most notably in infants, France prohibited BPA in plastic infant feeding bottles as a precautionary measure. This prohibition was then applied in all of Europe in 2011. Since 2015, BPA has been prohibited in all food contact materials in Europe and the European Food Safety Authority (EFSA) defined the maximum tolerable daily intake (TDI) for BPA at 4 µg/kg of body weight *per* day [20].

In the USA, the Food and Drug Administration (FDA) banned the presence of BPA in products designed for infants and toddlers in 2012 and in 2014 published a draft assessment of the available literature and data on BPA. This draft assessment indicated that the “no observed adverse effect level” (NOAEL) was 5 mg/kg of body weight per day without any definition of a total daily intake (TDI). In contrast, Japan adopted a similar TDI as the EFSA [21]. After a study reviewing the health risk assessment of BPA from food packaging applications in 2013, the Minister of Health of Canada recommended that the general principle

of ALARA (as low as reasonably achievable) should be applied to continue efforts to limit BPA exposure[22].

Therefore, despite that the majority of health authorities in the world have enacted policies limiting BPA exposure in their populations, there is a clear lack of international harmonization concerning the BPA limit of exposure. This lack, as mentioned by the WHO, is due in part to a lack of data from experimental animal studies that are suitable for risk assessment, but also to design and analysis issues in epidemiological studies and their resulting controversial results [23].

## 2 - BPA exposure

Due to the ubiquitous presence of BPA in the environment, all routes of exposure need to be considered to identify all sources of BPA, which is difficult process. Oral exposure seems to be the most frequent source of BPA exposure in the literature, notably through food contamination by containers. For example, aluminum cans can release BPA in food after the pasteurization process. In addition, it has been demonstrated that increased temperature and extended use of plastic baby bottles can increase polycarbonate hydrolysis and lead to a release of BPA in the bottle contents [24]. All plastic baby bottles containing BPA are now prohibited in numerous countries in Europe, as well as Canada, USA and China.

BPA can also be released from epoxy resin lining of pipes leading to an increase of BPA levels in drinking water [25]. Consequently, BPA has been found in drinking water at concentrations ranging from 0.014 to 0.317 µg/L and in water bottles at concentrations from 0.07 to 4.21 µg/L [26,27]. Furthermore, human exposure to BPA can occur from non-dietary sources such as air (indoor and outdoor), cosmetics, thermal paper, dust, toys, cars and more [15,28].

Because BPA production is currently very prominent it is inevitably found in the environment. The degradation half-life of BPA in soils ranges from 1 to 10 days depending on soil composition and temperature [29–31]. Thus, BPA is not considered a persistent organic pollutant (POP) but its presence in sediments and urban ecosystems underlines the necessity to decrease both plastic pollution and BPA production, and to increase plastic recycling.

BPA is found in human serum throughout the general population in levels ranging from 0.0002 to 66 ng/mL [32–35]. Moreover, it is also found in umbilical blood at levels of 0.5 to 52.26 µg/L reflecting both a maternal and a fetal exposure [36–38]. Administered orally, BPA is rapidly absorbed reaching a maximum blood concentration within 2 hours and has a

half-life time of approximately 6 hours [39,40]. Over 90 % of BPA is metabolized into BPA glucuronide (BPA-G) and it has been suggested that BPA phase II metabolism occurs in the small intestine [41–43]. The kinetic behavior of BPA-G appears more complex than BPA because of a prolonged terminal phase due to renal reabsorption [44]. BPA elimination occurs in a two-compartment model manner and the kidneys are the main way of elimination with a total elimination after 24 hours.

BPA is now well characterized as an ED but its glucuronide conjugate does not show estrogenic activity [45,46]. However, BPA-G has been shown to induce adipogenesis through an ER-independent pathway, confirming the complexity of the effects of BPA exposure [47].

### 3 - Impact of BPA in obesity

#### *Epidemiological studies*

Several recent reviews have been published concerning epidemiological data and the link between BPA exposure and obesity [39,48–51].

Rochester JR et al. (2013) reviewed the literature up to 2013 of BPA and its effects on human health and described that obesity and body weight were two of the most studied endpoints [8]. Nine of the ninety one articles analyzed reported that higher urinary or blood BPA concentration was significantly correlated with higher BMI or body weight [8]. However, because of the cross-sectional nature of these studies and controversial data, Rochester JR concluded that causal links may be complex and consequently difficult to interpret [8]. Lakind JS *et al.* (2014) reviewed the literature concerning the association of BPA exposure and diseases like obesity, diabetes and cardiovascular events. In this review, nine articles were selected that did not give evidence of a positive association between BPA exposure and obesity, BMI, waist circumference and body weight. Moreover, this review included studies carried out at single time point in adults, children and pregnant women and made interpretations for this population. This review also highlighted some controversial data [48]. Mirmira P and Evans-Molina C (2014) summarized human epidemiologic studies that have investigated links between BPA levels and obesity. Ten articles were selected that primarily showed associations between urinary BPA levels and obesity. However, no information about the criteria of selection of the articles was given and this work also highlights a number of caveats and controversies that should be considered in the article's interpretation [49]. Oppeneer S and Robien K (2015) supplied a detailed analysis and review of literature concerning the obesogenic activity of BPA

in humans. Eighteen studies were selected but evidence was unclear regarding the association between BPA exposure and increased BMI [50]. Most recently, Stojanoska MM *et al.* (2016) analyzed selected epidemiological studies of the effects of BPA on obesity and concluded that BPA has an indisputable role in the development of obesity in humans of BPA [39]. Collectively, all these reviews conclude: first, that BPA exposure may be involved in the development of obesity, however, that epidemiological data currently available are not sufficient to determine a positive correlation between high BPA exposure and obesity, second, that some results are divergent even when discussing controversies in the association of BPA and obesity and third, that significant limitations in methods do not currently permit a true meta-analysis.

However, as described above, obesity is a pathological condition with excessive fat mass. Adipose tissue is now considered an endocrine organ that actively secretes a number of adipokines. Zhao H.Y. *et al.* (2012) highlighted that high BPA exposure was associated with higher urinary levels of leptin, an adipokine that acts to induce satiety and regulates long term energy balance [52]. Elevated leptin levels contribute over time to the development of leptin resistance, a contributing factor to increase in fat mass [53,54]. More recently, Rönn M. *et al.* (2014) showed that increased adiponectin, an adipokine secreted in order to counteract insulin resistance, and leptin circulating levels were associated with an increased BPA level even without an increase in fat mass. In this study, which was performed with 870 subjects >70 years of age, elevated BPA levels were also associated with a decrease in ghrelin level [55]. Ghrelin is a hormone released from organs of the digestive system and from the hypothalamus and possesses orexigenic activity. Ghrelin is also known as a short and long term regulator of body weight and low ghrelin levels are associated with obesity in human patients [56,57]. Thus, these studies suggest that elevated BPA exposure is associated with changes in adipokine levels that are involved in regulation of appetite and satiety and generally associated with the pathophysiology of obesity. From these data it seems that adipose tissue is a target of BPA and produces adipocyte dysfunction.

#### *Limitations for epidemiological studies*

In epidemiological cross-sectional studies, BPA exposure is assessed by urine collection or serum dosages. The pharmacokinetic elimination of BPA is a two compartment model with a half-life of approximately 6 hours and a total elimination after 24 hours [40]. In addition, BPA is ubiquitously present in the atmosphere but its concentration considerably changes following



the seasons [58]. Thus, huge variations of BPA levels in the environment is a limitation for studying BPA exposure. Indeed, the general population is exposed to very low BPA doses through several routes of exposure and levels of BPA fluctuate throughout the life time. Given the pharmacokinetic properties of BPA, and that urinary dosage is generally measured by morning urine collection, measurements mainly display BPA exposure of the day before and only this day. Ye X *et al.* (2011) performed urinary BPA measurements on eight subjects continuously for one week. They observed a high within-person variability for urinary BPA concentrations accompanied with an important inter-variability [59]. In addition, dietary factors must be considered for epidemiological studies interpretations. Indeed, higher food intake is associated with a higher risk for BPA as well as obesity [50,51].

Thus, only longitudinal and prospective studies would supply sufficient information to draw conclusions regarding the obesogenic activity of BPA in adulthood.

*Infant / in utero exposure*

Because BPA is classified as an ED, the developmental periods that include prenatal, infancy and childhood are critical windows with increased sensitivity to BPA effects and exposure can lead to endocrine perturbations and metabolic disorders [51]. Several epidemiological studies regarding early-life exposure to BPA are available (Table I).

Table I: Summary of epidemiological studies regarding prenatal and early-life exposure to BPA

Country and cohort	Age or status of subjects (n)	BPA dosages (technique)	↗ BPA level was associated with: (main results)	Ref.
USA (NHANES 2003 - 2008) Cross sectional	6 – 19 y.o. (2838)	1 spot urine sample (HPLC-MS/MS)	Obesity for all ages and sex but only for non-Hispanic white children	Trasande L. <i>et al.</i> (2011) [60]
China (2011) Cross sectional	8 – 15 y.o. (259)	1 spot urine sample (HPLC-MS/MS)	↗ BMI after adjustment for age and sex	Wang H. <i>et al.</i> (2012) [61]
USA (CHAMACOS 2000 - 2010) Longitudinal	Pregnant women (402) 5 y.o. (319) 9 y.o. (311)	1 spot urine sample (HPLC-MS/MS) Prenatal (1 <sup>st</sup> and 3 <sup>rd</sup> trimester) Children 5 y.o. Children 9 y.o.	9 y.o., BPA prenatal exposure: ↘ BMI z-score and %BF only for girls  9 y.o.: ↗ BMI z-score, WC and %BF for both sex	Harley KG. <i>et al.</i> (2013) [62]
USA (NHANES 2003 - 2008) Cross sectional	6 – 18 y.o. (2200)	1 spot urine sample (HPLC-MS/MS)	↗ BMI for both sex and predominantly in non-Hispanic white boys	Bhandari R. <i>et al.</i> (2013) [63]
China (2011)	9 – 18 y.o. (1326)	1 spot urine sample (HPLC-FD)	↗ BW, HC, WC, waist-to-height ratio, ST and BMI only for girls aged from 9 to 12	Li DK. <i>et al.</i> (2013) [64]
USA (NHANES 2003 - 2010) Cross sectional	6 – 18 y.o. (3370)	1 spot urine sample (HPLC-MS/MS)	↗ BMI and waist-to-height ratio	Eng DS. <i>et al.</i> (2013) [65]
USA (NHANES 2003 - 2010) Cross sectional	6 – 18 y.o. (2836)	1 spot urine sample (HPLC-MS/MS)	↗ waist-to-height ratio only for boys and non-Hispanic children	Wells EM. <i>et al.</i> (2010) [66]
South Korea (2011)	6 – 14 y.o. (127, girls)	1 spot urine and 1 spot serum samples (GC-MS)	No differences for anthropometric measurements	Choi J. <i>et al.</i> (2014) [67]

France (EDEN 2002 – 2006)	520 mother-child pairs (boys only)	1 spot urine sample (HPLC-MS/MS) 3 <sup>rd</sup> trimester of pregnancy Children 3 y.o.	No differences for anthropometric measurements	Philippat C. <i>et al.</i> (2012) [68]
USA (HOME 2003 - 2006)	297 mother-child pairs	1 spot urine sample (HPLC-MS/MS) 2 <sup>nd</sup> and 3 <sup>rd</sup> trimester of pregnancy Children 2 – 5 y.o.	No differences for anthropometric measurements	Braun JM. <i>et al.</i> (2014) [69]
India (2012 – 2013)	2 – 14 y.o. (76)	1 spot urine sample (HPLC-MS/MS)	Obese and overweight children have lower BPA urinary levels	Xue J. <i>et al.</i> (2015) [70]
Spanish (INMA 2004 – 2006)	Pregnant women (470) 7 y.o. (470)	1 spot urine sample (HPLC-MS) 3 <sup>rd</sup> trimester of pregnancy	No differences for anthropometric measurements	Agay-Shay K. <i>et al.</i> (2015) [71]
Greece (Crete) (Rhea 2007 – 2008)	Pregnant women (235) 2.5 y.o.(235) 4 y.o. (500)	1 spot urine sample (HPLC-MS) 1 <sup>st</sup> trimester of pregnancy Children 2.5 y.o. Children 4 y.o.	4 y.o.: ↗ BMI z-score, WC and ST for boys but ↘ for girls 4 y.o.: ↗ BMI z-score, WC, ST.	Vafeiadi M. <i>et al.</i> (2016) [72]
USA (CCCEH 1999 – 2013) Longitudinal	Pregnant women (369) 3 y.o. (408) 5 y.o. (518) 7 y.o. (325)	1 spot urine sample (HPLC-MS/MS) 3 <sup>rd</sup> trimester of pregnancy Every 3 months until 3 y.o. then every 6 months	7 y.o.: ↗ FMI, %BF, WC with a sex-specificity for girls for FMI. No change in BMI z-score	Hoepner LA. <i>et al.</i> (2016) [73]

%BF: % of Body Fat, BMI: Body Mass Index, BW: Body Weight, FMI: Fat Mass Index, HC: Having Weight, ST: Skinfold Thickness, WC: Waist Circumference

Collectively, most data from epidemiological studies performed in adulthood (11/16) indicates that BPA exposure during developmental periods is associated with an increased risk of programmed obesity. However, the presence of studies showing no association or an opposite correlation does not allow this to be a definitive conclusion. In agreement with Braun JM (2016), we observed that available epidemiological data concerning the obesogenic activity of BPA is ambiguous [51]. Indeed, there are multiple sources of BPA exposure and obesity is a complex pathology for which the definition is still debated [74–76]. Moreover, evaluation of obesity in infants and children appears to be imprecise, notably by the disregard of additional parameters such as height. Thus, epidemiological studies should be more focused on other metabolic disorders such as glucose tolerance, insulin resistance, triglycerides and cholesterol levels, adipokines secretion and inflammatory markers such as circulating cytokines [39,77,78].

Such markers of metabolic disorders play an important role in adipose tissue development and energy homeostasis and may be more accurate for the characterization of the link between BPA exposure and the pathophysiology of obesity.

*In vivo studies*

Numerous studies have been published concerning the pathophysiology of obesity after BPA exposure in animals. In most of these reports, mice or rats were used and treated daily with 5 to 5000 µg/kg BPA by gavage or in drinking water for 4 weeks to 8 months. Conversely to the epidemiological trend, no increase in body weight was observed at the end of these experiments with BPA supplementation [79–82]. Nevertheless, animals treated with low doses of BPA presented metabolic dysfunctions associated with obesity including increased expression of genes involved in fatty acid metabolism, cholesterol and triglyceride biosynthesis [79]. These metabolic disorders are also found in animals fed with high fat diet (HFD) compared to animals fed with standard diet [82].

It has also been reported that BPA exposure induces disorders of the gut microbiota. In mice, BPA induces gut dysbiosis and the BPA-associated alterations of the microbiota were similar to those altered by HFD or high sucrose diet (HSD) [83,84]. Furthermore, because BPA is an environmental compound and a component of plastic cans, the BPA-dietary exposure has been evaluated in dogs fed with canned dog food. In this study, the authors reported a correlation between a higher BPA serum concentration and gut microbiome changes [85]. The gut microbiota has been identified as a sensor and a regulator of energy homeostasis that can communicate with peripheral organs such as brain, liver and adipose tissue and can eventually lead to the development of obesity [86,87]. Thus, even if the association between an increased body weight and an increased BPA exposure is not clear from animal studies, it is perfectly demonstrated that BPA can lead to metabolic and gut microbiota disorders that are directly linked with obesity.

Moreover, epidemiological studies show that the impact of BPA exposure in the pathophysiology of obesity is mostly explained by prenatal exposure (Table II).

Animal species	Dose, route of exposure	Food	Window of exposure	Weight change and age following the sex		Others effects regarding the pathophysiology of obesity	Ref.
				M	F		
Mice (CF-1)	2 et 20 µg/kg/d, gavage	Standard + 6,5% soja	GD11-17	↑ PND185	= PND23-310		Ashby J. <i>et al.</i> (1999) [88]
Mice (CF-1)	0.2-2-20-200 µg/kg/d, gavage	Standard	GD11-17	↑ PND36-90			Cagen SZ. <i>et al.</i> (1999) [89]
Rat (Wistar)	0.01-0.1-1.0-10 ppm, drinking water	Standard	WPM2-PND22	=PND90			Cagen SZ. <i>et al.</i> (1999) [90]
Mice (CF-1)	2,4 µg/kg/d, gavage		GD11-17	↑ PND22	↑ PND22		Howdeshell KL. <i>et al.</i> (1999 and 2000) [91,92]
Rat (SD)	0.1-1.2 mg/kg, drinking water	Standard	GD6-PND21	↑ PND4-110	↑ PND4-110		Rubin BS. <i>et al.</i> (2011) [93]
Mice (ICR/Jcl)	2-20 µg/kg/d, SC	Standard	GD11-17	↓ PND0-60	↓ PND0-60		Honna S. <i>et al.</i> (2002) [94]
Mice (C57Bl6/N)	2-20-200 µg/kg/d, gavage	Standard	GD11-17	= PNW12			Nagao T. <i>et al.</i> (2002) [95]
Rat (LE)	2.4 µg/kg/d, gavage	Standard	GD12-PND21	↑ PND90			Akingbemi BT. <i>et al.</i> (2004) [96]
Mice (CD-1)	0.5-10 mg/kg/d, SC	Standard	GD15-18		↑ PNW16		Nikaido Y. <i>et al.</i> (2004) [97]
Mice (ICR)	1-10 µg/kg/d, drinking water	High fat	GD10-PND31	↑ PND30	↑ PND30	M: ↑ adipose tissue weight, ↑ TG F: ↑ adipose tissue weight, ↑ total cholesterol	Miyawaki J. <i>et al.</i> (2007) [98]
Rat (LE)	2-20-200 µg/kg/d, gavage	Standard	GD7-PND18	= PND150			Howdeshell KL. <i>et al.</i> (2008) [99]
Animal species	Dose, route of exposure	Food	Window of exposure	Weight change and age following the sex		Others effects regarding the pathophysiology of obesity	Ref.
				M	F		
Rat (SD)	1 mg/l, drinking water	Standard during gestation, standard or high fat after birth	GD6-PND21	↑PNW9-14 For the high fat diet group	↑PND1-PNW14 For both groups	F: ↑ white and brown adipose tissue weight, adipocyte hypertrophy, overexpression of lipogenic genes	Somm E. <i>et al.</i> (2009) [100]

Mice (OF-1)	10-100 µg/kg/d, SC	Standard	GD9-16	= PND22- 180	↓PND22- 180	M: ↑ insulin resistance, ↓ glucose tolerance, ↑ plasma insulin, ↑ TG, ↑ plasma leptin	Alonso- Magdalena P. <i>et al.</i> (2010) [101]
Mice (CD-1)	1 µg/kg/d, food	Standard, high fat from SPN9	GD0- PND21	= PNW14	= PNW14		Ryan KK. <i>et al.</i> (2010) [102]
Rat (Wistar)	50-250-1250 µg/kg/d, gavage	Standard or high fat	GD0- PND21	↑PNW3- 26	↑PNW3- 26	M + F: ↑ serum insulin, ↓ glucose tolerance, ↑ adipocyte hypertrophy	Wei J. <i>et al.</i> (2011) <sup>o</sup> [103]
Mice (Agouti a/a)	0.05-50- 50 000 µg/kg/d, food	Standard	2 w. before coupling- PND22	=PNM3- 9	↓PNM3- 9	M + F: ↑ energy expenditure F: ↓ Fat mass	Anderson OS. <i>et al.</i> (2013) [104]
Mice (CD-1)	5-50-500- 5 000-50 000 µg/kg/d, gavage	Standard	GD9-16	↑ PND0- PNW19		M: ↑ abdominal fat weight, adipocyte hyperplasy and hypertrophy, ↑ serum insulin and leptin, ↓ serum adiponectin, ↓ glucose tolerance	Angle BM. <i>et al.</i> (2013) [105]
Mice (C57Bl6)	100 µg/kg/d, SC	Standard	GD6- PND0 PND0-21 GD6- PND21	↓ PNM3-8 ↑ PNM3-8 = PNM3-8		↓ glucose tolerance ↓ glucose tolerance ↓ glucose tolerance	Liu J. <i>et al.</i> (2013) [106]
Mice (C57Bl6/JxFVB)	3-10-30-100- 300-1 000- 3 000 µg/kg/d, food	Standard High fat for F PNW17-21	2 w. before coupling- PND21	↑ PNW6- 21	↓ PNW8- 21	M: ↓ serum glucagon, ↓ physical activity, adipocyte hypertrophy F: ↓ adipose tissue weight, ↓ TG, ↓ serum leptin and adiponectin	Van Esterik JCI. <i>et al.</i> (2014) [107]
Animal species	Dose, route of exposure	Food	Window of exposure	Weight change and age following the sex		Others effects regarding the pathophysiology of obesity	Ref.
				M	F		
Mice (California)	50 mg/kg of food	Low phytoestrogen AIN93G	2 w. before coupling- PND30	= PND90	= PND90	F + M: ↓ voluntary physical activity, = serum glucose, insulin, leptin and adiponectin	Johnson SA. <i>et al.</i> (2015) [108]
Mice (CD-1)	0.25, 2.5, 25, or 250 µg/kg/d, osmotic pump (dams), drinking water (peripubertal)	Standard	GD8- PND16 PND21-35	↑ PNW43	↑ PNW43	M: ↑ adiposity F: ↑ serum glucose and insulin, insulin resistance, ↑ serum leptin, ↑ TG,	Rubin BS. <i>et al.</i> (2016) [109]
Mice (OF-1)	10-100 µg/kg, SC	Standard	GD9-16	↑ PND120		↑ serum insulin, ↑ serum leptin,	García- Arévalo M <i>et al.</i>

							(2016) [110]
Rat (SD)	1-10 µg/mL, drinking water	Standard	GD6- PND21	↑ PND50	↑ PND50	M: ↑ perirenal adipose tissue F: ↑ perigonadal adipose tissue M + F: ↑ TG, ↑ total cholesterol	Gao L. <i>et al.</i> (2016) [111]
M, male; F, female; GD, gestation day; PND, post-natal day; PNW, post-natal week; PNM, post-natal month; SC, subcutaneous; TG, triglycerides; WPM: week prior mating.							

Table II depicts that a majority of studies, although notably not all (13/24 for males and 8/15 for females), reported an association between prenatal exposure of BPA and an increased body weight of animal pups. Some studies also reported no association (8/24 for males and 3/15 for females) and others reported an inverse correlation (2/24 for males and 4/15 for females). These divergent results, as in the epidemiological studies, raise concerns about the data and do not allow definitive conclusions. The central difficulty is the variability of methods that differ in terms of doses, window of exposure and age of animal pups at the end of the experiments. Despite a large library of available literature, one cannot identify a precise window and dose of exposure to BPA that is responsible for an increased risk to develop obesity. Liu J. *et al.* (2013) well demonstrated the differences in body weight variations of mice between different windows of exposure (prenatal, lactation or both) for the same dose of BPA [106].

BPA is classified as an ED and consequently obeys the new paradigms of toxicology. Parameters like the latency of effects, timing and sensitivity as well as the sex should be considered during experiments. Additionally, because very low doses of BPA are potentially sufficient to produce an effect and because BPA is readily found in the environment, the relevance of the control group in these studies may be questioned. Indeed, how can it be attested that the control group is a non-exposed group while BPA is detected in animal cages and drinking water [27,112–114] ? Thus, the blood concentration of BPA has to be checked for all groups for each experiment to improve stringency in these studies. In light of these observations, meta-analyses, by examination of heterogeneity and identification of sources of variations, now appears to be a relevant way to supply the strength of evidence characterizing the association between BPA exposure and the development of obesity.

Despite the outlying reports, a majority of these studies indicates a positive association between prenatal BPA exposure and metabolic disorders, notably concerning adiposity and glucose and lipid homeostasis. A dysregulation of adipokine secretion can lead to adipocyte dysfunction and be involved in obesity-induced inflammation and insulin resistance [115]. Leptin is a hormone targeting the hypothalamus in order to inhibit orexigenic neurons and ultimately inducing satiety [116]. Obesity is associated with leptin resistance and high serum leptin levels [117,118]. Adiponectin is an adipocyte-derived hormone capable of targeting several tissues in order to increase insulin sensitivity [115]. In table II and in line with epidemiological data, prenatal exposure of BPA in animals enhances serum leptin levels and decreases serum adiponectin level in association with the pathophysiology of obesity.



In addition, type 2 diabetes is a major comorbidity of obesity and includes, at least, in part, a decrease in glucose tolerance, insulin resistance and elevated plasma insulin levels. As indicated in table II, prenatal exposure to BPA induces glucose homeostasis disorders, a predisposition to diabetes and a sustained obesogenic activity.

#### *In vitro studies*

Epidemiological and animal studies reveal that BPA exposure leads to perturbations in adipokine secretion and to adipocyte dysfunction suggesting that the adipose tissue is a central target of BPA activity. *In vitro* studies have identified molecular targets and signaling pathways that may be involved in the pathogenesis of obesity after BPA exposure. The effect of BPA in metabolic and endocrine disorders has already been reviewed on endoderm-derived organs (thyroid, pancreas, liver, gut, prostate and lung) [119]. However, the following are delineated *in vitro* results from studies examining BPA effects in adipocyte function.

Masuno H. *et al.* demonstrated that BPA treatment (8.8  $\mu$ M, 2 mg/L) in murine 3T3-L1 fibroblasts before and after the adipocyte differentiation stimulus increases triacylglycerol (TG) content, LPL activity and GPDH activity, two enzymes involved in lipid metabolism [120]. Thus, BPA exposure induces adipocyte differentiation and increases intra-cytosolic lipid accumulation. Similarly, Ohlstein J.F. *et al.* demonstrated that 1  $\mu$ M for 21 days was able to enhance adipogenesis of human adipose stromal/stem cells (ASCs) [121]. These results indicate that BPA, in a  $\mu$ M concentration range, induces adipocyte differentiation. In another study, Valentino R. *et al.* exposed differentiated 3T3-L1 to 1 nM of BPA for 48 hours. They noted that BPA exposure under this treatment condition decreased adipocyte insulin sensitivity [122]. These results were associated with a decrease of Glucose Transporter 1 (GLUT1) expression, insulin receptor phosphorylation and overall insulin sensitivity, suggesting that BPA also induces disorders in glucose metabolism and may increase the risk of type 2 diabetes, a devastating complication in many obese patients [122,123]. In addition, BPA increases IL-6 and IFN- $\gamma$  expression and activates the pro-inflammatory JNK/STAT3/NF $\kappa$ B pathway [122,124]. All together, these results suggest that BPA, in a  $\mu$ M concentration range, induces adipocyte differentiation, and in a nM concentration range, induces an adipocyte dysfunction reflected by a decrease in insulin sensitivity and a stimulation of pro-inflammatory responses.

Several molecular targets have been identified to explain the obesogenic effect of BPA [39,51,125]. Indeed, it has been reported that BPA, in concentration ranges of  $\mu$ M, interacts with Nuclear Receptors (NR), Estrogen Receptors (ER), Glucocorticoid Receptors (GR),

peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ), the Retinoid X Receptor (RXR) and Thyroid Receptors (TR) [126–129]. All these receptors are involved in adipogenesis [130–134]. By activating these receptors, BPA may promote adipocyte differentiation and increases in lipid storage.

Furthermore, activation of C/EBP- $\alpha$ , LPL and mammalian Target Of Rapamycin (mTOR), which are involved in lipogenesis and adipokine secretion, has also been described after adipocyte exposure to BPA, concurrent with a decrease of adiponectin secretion [121,126,128,135]. Thus, BPA induces inflammatory activation, adipogenesis and lipogenesis pathways and modulates adipokine secretion contributing to adipocyte dysfunction, which may explain lipid accumulation and the increase of fat mass observed (Figure 2). These results are in agreement with those from human and animal studies and confirm the impact of BPA exposure on adipocyte dysfunction found in obesity.

Interestingly, most BPA is metabolized to BPA-G initially. Boucher J.G. *et al.* evaluated the effect of 10 $\mu$ M of BPA-G on the differentiation of human and 3T3L1 murine preadipocytes. They demonstrated that BPA-G was able to promote adipocyte differentiation and that this effect was associated with an increase of mRNA of sterol regulatory element binding factor 1 (SREBF1), LPL, protein levels of LPL, aP2, and adipsin, all adipogenic markers [47]. These results indicate that not only BPA but also its predominant metabolite are able to induce adipocyte differentiation.

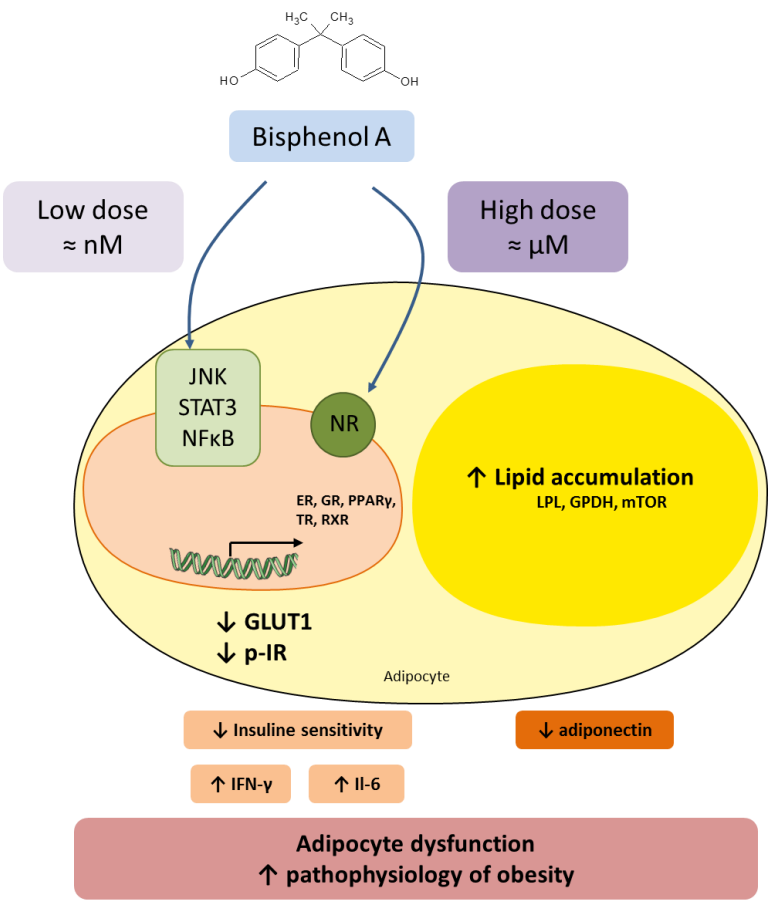


Figure 2: Signaling pathways activated by low and high doses of BPA during adipocyte differentiation.

Epigenetics:

Several data have demonstrated the ability of BPA to induce genetic modifications with dramatic consequences on reproductive functions and cancer development [136,137]. However, available data regarding the impact of BPA exposure on genetic aspects of obesity remains sparse so far. Among genome-wide association studies (GWAS) findings, the locus *fat mass and obesity associated (FTO)* was described as the most associated gene with an increased BMI, each risk allele of this locus increasing risk of obesity from 20 % to 30 % in humans [138–141]. Other genes regulating expression of signaling molecules involved in glucose and lipid homeostasis and in feeding behavior were also identified such as those encoding *melanocortin receptors (MCRs)*, *proopiomelanocortin (POMC)*, *Agouti* or *brain-derived neurotrophic factor (BDNF)* [140]. The regulation of gene expression is predominantly mediated by DNA methylation, RNA silencing, histone acetylation and nucleosome remodeling, four epigenetic mechanistic processes [142–144]. In the viable yellow Agouti (A

<sup>yy</sup>) mouse model, fetal exposure of BPA decreases methylation of the *Agouti* promoter, leading to a statistically significant shift in offspring coat color phenotype toward yellow [145]. In addition, in an embryonic mouse hypothalamus cell line, BPA alters gene expression levels that can be linked to the observed BDNF modification of expression [146]. These results suggest that BPA fetal exposure induces epigenomic alterations in genes involved in the pathophysiology of obesity, thus confirming the *in utero* programming of obesity after BPA exposure, as described in animal and epidemiological studies [147].

## CONCLUSION and PERSPECTIVES

Despite its rapid elimination time, the ubiquitous presence of BPA in our environment ensures that humans are continuously exposed. This review of the available literature favors the conclusion that BPA should be considered an obesogenic environmental compound. Metabolic disorders or adipocyte dysfunctions are described in epidemiological, animal and *in vitro* studies following BPA exposure. In addition, the effects of BPA on obesity development should thus be measured not only by BMI but also by contribution to adipogenesis, lipid and glucose dysregulation and adipose tissue inflammation. Although some data in the literature remains controversial regarding the link between BPA and obesity, evidence continues to grow that EDs like BPA are involved in the huge rise of the obesity epidemic. Meta-analyses conducted on data obtained from the current literature are now needed to definitively answer on the effects of BPA on obesity.

Due to increased evidence regarding the deleterious effects of BPA, numerous alternatives to BPA for use in manufacturing have arisen such as bisphenol AF (BPAF), bisphenol B (BPB), bisphenol F (BPF), bisphenol S (BPS) and 4-cumylphenol (HPP). These compounds are gradually replacing BPA in plastics and thermal paper. However, it has been confirmed these compounds have an estrogenic and androgenic activity *in vitro*, indicating they have similar endocrine disrupting capability than BPA and distribute to the body and are also a concern for fetal exposure during pregnancy [148–151]. However, data remains sparse as to whether or not these alternative compounds contribute to adipocyte dysregulation, and subsequently, obesity. BPS, BPA analog used for thermal paper, is the only compound among these BPA alternatives that has been shown to exert obesogenic activity in mice and *in vitro* as evidenced by an association with increased body weight, perturbations in adipokine secretion and in dysregulation of glucose homeostasis [152–154]. These data clearly support the urgent need to both decrease human bisphenol exposure and to find new alternative compounds for the plastic manufacturing.

Importantly, the role of EDs in the growth of the obesity epidemic worldwide is now well established [155,156]. However, the contribution of each suspected obesogen in this epidemic remains unclear, likely because of synergistic effects between all of these chemicals. Additional studies evaluating the effects of environmental obesogens are now needed and would offer new tools for the prevention of obesity.

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## REFERENCES

1. WHO | Challenges [Internet]. WHO. [cited 2017 Jan 30]. Available from: <http://www.who.int/nutrition/challenges/en/>
2. Dhurandhar NV, Schoeller D, Brown AW, Heymsfield SB, Thomas D, Sørensen TIA, et al. Energy balance measurement: when something is not better than nothing. *Int J Obes*. 2015 Jul;39(7):1109–13.
3. Baillie-Hamilton PF. Chemical toxins: a hypothesis to explain the global obesity epidemic. *J Altern Complement Med N Y N*. 2002 Apr;8(2):185–92.
4. Holtcamp W. Obesogens: An Environmental Link to Obesity. *Environ Health Perspect*. 2012 Feb;120(2):a62–8.
5. Kelishadi R, Poursafa P, Jamshidi F. Role of environmental chemicals in obesity: a systematic review on the current evidence. *J Environ Public Health*. 2013;2013:896789.
6. Colborn T, vom Saal FS, Soto AM. Developmental effects of endocrine-disrupting chemicals in wildlife and humans. *Environ Health Perspect*. 1993 Oct;101(5):378–84.
7. WHO | State of the science of endocrine disrupting chemicals - 2012 [Internet]. WHO. [cited 2017 Jan 6]. Available from: <http://www.who.int/ceh/publications/endocrine/en/>
8. Rochester JR. Bisphenol A and human health: a review of the literature. *Reprod Toxicol Elmsford N*. 2013 Dec;42:132–55.
9. Chevalier N, Fénichel P. Bisphenol A: Targeting metabolic tissues. *Rev Endocr Metab Disord*. 2015 Dec 1;16(4):299–309.
10. Janesick AS, Blumberg B. Obesogens: an emerging threat to public health. *Am J Obstet Gynecol*. 2016 May;214(5):559–65.
11. Kirchner S, Kieu T, Chow C, Casey S, Blumberg B. Prenatal exposure to the environmental obesogen tributyltin predisposes multipotent stem cells to become adipocytes. *Mol Endocrinol Baltim Md*. 2010 Mar;24(3):526–39.
12. Grün F, Watanabe H, Zamanian Z, Maeda L, Arima K, Cubacha R, et al. Endocrine-disrupting organotin compounds are potent inducers of adipogenesis in vertebrates. *Mol Endocrinol Baltim Md*. 2006 Sep;20(9):2141–55.
13. Grün F, Blumberg B. Perturbed nuclear receptor signaling by environmental obesogens as emerging factors in the obesity crisis. *Rev Endocr Metab Disord*. 2007 Jun;8(2):161–71.
14. Legler J. An integrated approach to assess the role of chemical exposure in obesity. *Obes Silver Spring Md*. 2013 Jun;21(6):1084–5.
15. Michałowicz J. Bisphenol A--sources, toxicity and biotransformation. *Environ Toxicol Pharmacol*. 2014 Mar;37(2):738–58.

- 459 16. Huang YQ, Wong CKC, Zheng JS, Bouwman H, Barra R, Wahlström B, et al. Bisphenol  
460 A (BPA) in China: a review of sources, environmental levels, and potential human  
461 health impacts. *Environ Int.* 2012 Jul;42:91–9.
- 462 17. Cao X-L, Corriveau J, Popovic S. Sources of low concentrations of bisphenol A in  
463 canned beverage products. *J Food Prot.* 2010 Aug;73(8):1548–51.
- 464 18. Dodson RE, Nishioka M, Standley LJ, Perovich LJ, Brody JG, Rudel RA. Endocrine  
465 disruptors and asthma-associated chemicals in consumer products. *Environ Health*  
466 *Perspect.* 2012 Jul;120(7):935–43.
- 467 19. Geens T, Goeyens L, Kannan K, Neels H, Covaci A. Levels of bisphenol-A in thermal  
468 paper receipts from Belgium and estimation of human exposure. *Sci Total Environ.* 2012  
469 Oct 1;435–436:30–3.
- 470 20. EFSA explains the Safety of Bisphenol A | European Food Safety Authority [Internet].  
471 [cited 2016 Aug 29]. Available from:  
472 <https://www.efsa.europa.eu/en/topics/factsheets/factsheetbpa150121>
- 473 21. Nutrition C for FS and A. Food Additives & Ingredients - Bisphenol A (BPA) [Internet].  
474 [cited 2016 Aug 29]. Available from:  
475 [http://www.fda.gov/Food/IngredientsPackagingLabeling/FoodAdditivesIngredients/ucm](http://www.fda.gov/Food/IngredientsPackagingLabeling/FoodAdditivesIngredients/ucm166145.htm)  
476 [166145.htm](http://www.fda.gov/Food/IngredientsPackagingLabeling/FoodAdditivesIngredients/ucm166145.htm)
- 477 22. Government of Canada HC. ARCHIVED - Health Risk Assessment of Bisphenol A  
478 from Food Packaging Applications [Internet]. 2008 [cited 2016 Aug 29]. Available  
479 from: [http://www.hc-sc.gc.ca/fn-an/securit/packag-embal/bpa/bpa\\_hra-ers-eng.php](http://www.hc-sc.gc.ca/fn-an/securit/packag-embal/bpa/bpa_hra-ers-eng.php)
- 480 23. WHO | Toxicological and health aspects of bisphenol A [Internet]. WHO. [cited 2016  
481 Aug 29]. Available from: <http://www.who.int/foodsafety/publications/bisphenol-a/en/>
- 482 24. Nam S-H, Seo Y-M, Kim M-G. Bisphenol A migration from polycarbonate baby bottle  
483 with repeated use. *Chemosphere.* 2010 May;79(9):949–52.
- 484 25. Rajasärkkä J, Pernica M, Kuta J, Lašňák J, Šimek Z, Bláha L. Drinking water  
485 contaminants from epoxy resin-coated pipes: A field study. *Water Res.* 2016 Oct  
486 15;103:133–40.
- 487 26. Arnold SM, Clark KE, Staples CA, Klecka GM, Dimond SS, Caspers N, et al. Relevance  
488 of drinking water as a source of human exposure to bisphenol A. *J Expo Sci Environ*  
489 *Epidemiol.* 2013 Mar;23(2):137–44.
- 490 27. Colin A, Bach C, Rosin C, Munoz J-F, Dauchy X. Is drinking water a major route of  
491 human exposure to alkylphenol and bisphenol contaminants in France? *Arch Environ*  
492 *Contam Toxicol.* 2014 Jan;66(1):86–99.
- 493 28. Geens T, Roosens L, Neels H, Covaci A. Assessment of human exposure to Bisphenol-  
494 A, Triclosan and Tetrabromobisphenol-A through indoor dust intake in Belgium.  
495 *Chemosphere.* 2009 Aug;76(6):755–60.
- 496 29. Kang J-H, Kondo F. Bisphenol A degradation in seawater is different from that in river  
497 water. *Chemosphere.* 2005 Sep;60(9):1288–92.



- 498 30. Fox JE, Gullledge J, Engelhaupt E, Burow ME, McLachlan JA. Pesticides reduce  
499 symbiotic efficiency of nitrogen-fixing rhizobia and host plants. *Proc Natl Acad Sci U S*  
500 *A*. 2007 Jun 12;104(24):10282–7.
- 501 31. Corrales J, Kristofco LA, Steele WB, Yates BS, Breed CS, Williams ES, et al. Global  
502 Assessment of Bisphenol A in the Environment: Review and Analysis of Its Occurrence  
503 and Bioaccumulation. *Dose-Response Publ Int Hormesis Soc*. 2015  
504 Sep;13(3):1559325815598308.
- 505 32. Sajiki J, Takahashi K, Yonekubo J. Sensitive method for the determination of bisphenol-  
506 A in serum using two systems of high-performance liquid chromatography. *J*  
507 *Chromatogr B Biomed Sci App*. 1999 Dec 24;736(1–2):255–61.
- 508 33. vom Saal FS, Welshons WV. Evidence that bisphenol A (BPA) can be accurately  
509 measured without contamination in human serum and urine, and that BPA causes  
510 numerous hazards from multiple routes of exposure. *Mol Cell Endocrinol*. 2014  
511 Dec;398(1–2):101–13.
- 512 34. Savastano S, Tarantino G, D’Esposito V, Passaretti F, Cabaro S, Liotti A, et al.  
513 Bisphenol-A plasma levels are related to inflammatory markers, visceral obesity and  
514 insulin-resistance: a cross-sectional study on adult male population. *J Transl Med*.  
515 2015;13:169.
- 516 35. Camarca A, Gianfrani C, Ariemma F, Cimmino I, Bruzzese D, Scerbo R, et al. Human  
517 Peripheral Blood Mononuclear Cell Function and Dendritic Cell Differentiation Are  
518 Affected by Bisphenol-A Exposure. *PLOS ONE*. 2016 Aug 10;11(8):e0161122.
- 519 36. Lee YJ, Ryu H-Y, Kim H-K, Min CS, Lee JH, Kim E, et al. Maternal and fetal exposure  
520 to bisphenol A in Korea. *Reprod Toxicol Elmsford N*. 2008 Aug;25(4):413–9.
- 521 37. Fénichel P, Déchaux H, Harthe C, Gal J, Ferrari P, Pacini P, et al. Unconjugated  
522 bisphenol A cord blood levels in boys with descended or undescended testes. *Hum*  
523 *Reprod Oxf Engl*. 2012 Apr;27(4):983–90.
- 524 38. Gerona RR, Woodruff TJ, Dickenson CA, Pan J, Schwartz JM, Sen S, et al. Bisphenol-A  
525 (BPA), BPA glucuronide, and BPA sulfate in midgestation umbilical cord serum in a  
526 northern and central California population. *Environ Sci Technol*. 2013;47(21):12477–85.
- 527 39. Stojanoska MM, Milosevic N, Milic N, Abenavoli L. The influence of phthalates and  
528 bisphenol A on the obesity development and glucose metabolism disorders. *Endocrine*.  
529 2016 Nov 7;
- 530 40. Völkel W, Colnot T, Csanády GA, Filser JG, Dekant W. Metabolism and Kinetics of  
531 Bisphenol A in Humans at Low Doses Following Oral Administration. *Chem Res*  
532 *Toxicol*. 2002 Oct 1;15(10):1281–7.
- 533 41. Fisher JW, Twaddle NC, Vanlandingham M, Doerge DR. Pharmacokinetic modeling:  
534 prediction and evaluation of route dependent dosimetry of bisphenol A in monkeys with  
535 extrapolation to humans. *Toxicol Appl Pharmacol*. 2011 Nov 15;257(1):122–36.
- 536 42. Mazur CS, Kenneke JF, Hess-Wilson JK, Lipscomb JC. Differences between human and  
537 rat intestinal and hepatic bisphenol A glucuronidation and the influence of alamethicin

- 538 on in vitro kinetic measurements. *Drug Metab Dispos Biol Fate Chem*. 2010  
539 Dec;38(12):2232–8.
- 540 43. Audebert M, Dolo L, Perdu E, Cravedi J-P, Zalko D. Use of the  $\gamma$ H2AX assay for  
541 assessing the genotoxicity of bisphenol A and bisphenol F in human cell lines. *Arch*  
542 *Toxicol*. 2011 Nov;85(11):1463–73.
- 543 44. Yang X, Fisher JW. Unraveling bisphenol A pharmacokinetics using physiologically  
544 based pharmacokinetic modeling. *Front Pharmacol*. 2014;5:292.
- 545 45. Snyder RW, Maness SC, Gaido KW, Welsch F, Sumner SC, Fennell TR. Metabolism  
546 and disposition of bisphenol A in female rats. *Toxicol Appl Pharmacol*. 2000 Nov  
547 1;168(3):225–34.
- 548 46. Elsbey R, Maggs JL, Ashby J, Park BK. Comparison of the modulatory effects of human  
549 and rat liver microsomal metabolism on the estrogenicity of bisphenol A: implications  
550 for extrapolation to humans. *J Pharmacol Exp Ther*. 2001 Apr;297(1):103–13.
- 551 47. Boucher JG, Boudreau A, Ahmed S, Atlas E. In Vitro Effects of Bisphenol A  $\beta$ -D-  
552 Glucuronide (BPA-G) on Adipogenesis in Human and Murine Preadipocytes. *Environ*  
553 *Health Perspect*. 2015 Dec;123(12):1287–93.
- 554 48. Lakind JS, Goodman M, Mattison DR. Bisphenol A and indicators of obesity, glucose  
555 metabolism/type 2 diabetes and cardiovascular disease: a systematic review of  
556 epidemiologic research. *Crit Rev Toxicol*. 2014 Feb;44(2):121–50.
- 557 49. Mirmira P, Evans-Molina C. Bisphenol A, obesity, and type 2 diabetes mellitus: genuine  
558 concern or unnecessary preoccupation? *Transl Res J Lab Clin Med*. 2014 Jul;164(1):13–  
559 21.
- 560 50. Oppeneer SJ, Robien K. Bisphenol A exposure and associations with obesity among  
561 adults: a critical review. *Public Health Nutr*. 2015 Jul;18(10):1847–63.
- 562 51. Braun JM. Early-life exposure to EDCs: role in childhood obesity and  
563 neurodevelopment. *Nat Rev Endocrinol*. 2016 Nov 18;
- 564 52. Zhao H, Bi Y, Ma L, Zhao L, Wang T, Zhang L, et al. The effects of bisphenol A (BPA)  
565 exposure on fat mass and serum leptin concentrations have no impact on bone mineral  
566 densities in non-obese premenopausal women. *Clin Biochem*. 2012 Dec;45(18):1602–6.
- 567 53. Pan H, Guo J, Su Z. Advances in understanding the interrelations between leptin  
568 resistance and obesity. *Physiol Behav*. 2014 May 10;130:157–69.
- 569 54. Mantzoros CS, Magkos F, Brinkoetter M, Sienkiewicz E, Dardeno TA, Kim S-Y, et al.  
570 Leptin in human physiology and pathophysiology. *Am J Physiol Endocrinol Metab*.  
571 2011 Oct;301(4):E567-584.
- 572 55. Rönn M, Lind L, Örborg J, Kullberg J, Söderberg S, Larsson A, et al. Bisphenol A is  
573 related to circulating levels of adiponectin, leptin and ghrelin, but not to fat mass or fat  
574 distribution in humans. *Chemosphere*. 2014 Oct;112:42–8.

- 575 56. Yildiz BO, Suchard MA, Wong M-L, McCann SM, Licinio J. Alterations in the  
576 dynamics of circulating ghrelin, adiponectin, and leptin in human obesity. *Proc Natl*  
577 *Acad Sci U S A*. 2004 Jul 13;101(28):10434–9.
- 578 57. Tschöp M, Weyer C, Tataranni PA, Devanarayan V, Ravussin E, Heiman ML.  
579 Circulating ghrelin levels are decreased in human obesity. *Diabetes*. 2001  
580 Apr;50(4):707–9.
- 581 58. Fu P, Kawamura K. Ubiquity of bisphenol A in the atmosphere. *Environ Pollut Barking*  
582 *Essex* 1987. 2010 Oct;158(10):3138–43.
- 583 59. Ye X, Wong L-Y, Bishop AM, Calafat AM. Variability of urinary concentrations of  
584 bisphenol A in spot samples, first morning voids, and 24-hour collections. *Environ*  
585 *Health Perspect*. 2011 Jul;119(7):983–8.
- 586 60. Trasande L, Attina TM, Blustein J. Association between urinary bisphenol A  
587 concentration and obesity prevalence in children and adolescents. *JAMA*. 2012 Sep  
588 19;308(11):1113–21.
- 589 61. Wang H, Zhou Y, Tang C, Wu J, Chen Y, Jiang Q. Association between bisphenol A  
590 exposure and body mass index in Chinese school children: a cross-sectional study.  
591 *Environ Health Glob Access Sci Source*. 2012 Oct 19;11:79.
- 592 62. Harley KG, Aguilar Schall R, Chevrier J, Tyler K, Aguirre H, Bradman A, et al. Prenatal  
593 and postnatal bisphenol A exposure and body mass index in childhood in the  
594 CHAMACOS cohort. *Environ Health Perspect*. 2013 Apr;121(4):514–20.
- 595 63. Bhandari R, Xiao J, Shankar A. Urinary bisphenol A and obesity in U.S. children. *Am J*  
596 *Epidemiol*. 2013 Jun 1;177(11):1263–70.
- 597 64. Li D-K, Miao M, Zhou Z, Wu C, Shi H, Liu X, et al. Urine bisphenol-A level in relation  
598 to obesity and overweight in school-age children. *PloS One*. 2013;8(6):e65399.
- 599 65. Eng DS, Lee JM, Gebremariam A, Meeker JD, Peterson K, Padmanabhan V. Bisphenol  
600 A and chronic disease risk factors in US children. *Pediatrics*. 2013 Sep;132(3):e637-645.
- 601 66. Wells EM, Jackson LW, Koontz MB. Association between bisphenol A and waist-to-  
602 height ratio among children: National Health and Nutrition Examination Survey, 2003-  
603 2010. *Ann Epidemiol*. 2014 Feb;24(2):165–7.
- 604 67. Choi J, Eom J, Kim J, Lee S, Kim Y. Association between some endocrine-disrupting  
605 chemicals and childhood obesity in biological samples of young girls: a cross-sectional  
606 study. *Environ Toxicol Pharmacol*. 2014 Jul;38(1):51–7.
- 607 68. Philippat C, Mortamais M, Chevrier C, Petit C, Calafat AM, Ye X, et al. Exposure to  
608 phthalates and phenols during pregnancy and offspring size at birth. *Environ Health*  
609 *Perspect*. 2012 Mar;120(3):464–70.
- 610 69. Braun JM, Lanphear BP, Calafat AM, Deria S, Khoury J, Howe CJ, et al. Early-life  
611 bisphenol a exposure and child body mass index: a prospective cohort study. *Environ*  
612 *Health Perspect*. 2014 Nov;122(11):1239–45.

- 613 70. Xue J, Wu Q, Sakthivel S, Pavithran PV, Vasukutty JR, Kannan K. Urinary levels of  
614 endocrine-disrupting chemicals, including bisphenols, bisphenol A diglycidyl ethers,  
615 benzophenones, parabens, and triclosan in obese and non-obese Indian children. *Environ*  
616 *Res.* 2015 Feb;137:120–8.
- 617 71. Agay-Shay K, Martinez D, Valvi D, Garcia-Esteban R, Basagaña X, Robinson O, et al.  
618 Exposure to Endocrine-Disrupting Chemicals during Pregnancy and Weight at 7 Years  
619 of Age: A Multi-pollutant Approach. *Environ Health Perspect.* 2015 Oct;123(10):1030–  
620 7.
- 621 72. Vafeiadi M, Roumeliotaki T, Myridakis A, Chalkiadaki G, Fthenou E, Dermitzaki E, et  
622 al. Association of early life exposure to bisphenol A with obesity and cardiometabolic  
623 traits in childhood. *Environ Res.* 2016 Apr;146:379–87.
- 624 73. Hoepner LA, Whyatt RM, Widen EM, Hassoun A, Oberfield SE, Mueller NT, et al.  
625 Bisphenol A and Adiposity in an Inner-City Birth Cohort. *Environ Health Perspect.* 2016  
626 Oct;124(10):1644–50.
- 627 74. De Lorenzo A, Soldati L, Sarlo F, Calvani M, Di Lorenzo N, Di Renzo L. New obesity  
628 classification criteria as a tool for bariatric surgery indication. *World J Gastroenterol.*  
629 2016 Jan 14;22(2):681–703.
- 630 75. Roth J, Sahota N, Patel P, Mehdi SF, Wiese MM, Mahboob HB, et al. Obesity paradox,  
631 obesity orthodox, and the metabolic syndrome: An approach to unity. *Mol Med Camb*  
632 *Mass.* 2016 Nov 16;22.
- 633 76. Stacy SL, Eliot M, Calafat AM, Chen A, Lanphear BP, Hauser R, et al. Patterns,  
634 Variability, and Predictors of Urinary Bisphenol A Concentrations during Childhood.  
635 *Environ Sci Technol.* 2016 Jun 7;50(11):5981–90.
- 636 77. Menale C, Grandone A, Nicolucci C, Cirillo G, Crispi S, Di Sessa A, et al. Bisphenol A  
637 is associated with insulin resistance and modulates adiponectin and resistin gene  
638 expression in obese children. *Pediatr Obes.* 2016 Jan 1;n/a-n/a.
- 639 78. Ashley-Martin J, Dodds L, Arbuckle TE, Ettinger AS, Shapiro GD, Fisher M, et al. A  
640 birth cohort study to investigate the association between prenatal phthalate and bisphenol  
641 A exposures and fetal markers of metabolic dysfunction. *Environ Health [Internet].* 2014  
642 [cited 2016 Nov 25];13. Available from: [https://www.ncbi.nlm-nih-](https://www.ncbi.nlm-nih-gov.gate2.inist.fr/pmc/articles/PMC4271497/)  
643 [gov.gate2.inist.fr/pmc/articles/PMC4271497/](https://www.ncbi.nlm-nih-gov.gate2.inist.fr/pmc/articles/PMC4271497/)
- 644 79. Marmugi A, Ducheix S, Lasserre F, Polizzi A, Paris A, Priymenko N, et al. Low doses  
645 of bisphenol A induce gene expression related to lipid synthesis and trigger triglyceride  
646 accumulation in adult mouse liver. *Hepatol Baltim Md.* 2012 Feb;55(2):395–407.
- 647 80. Marmugi A, Lasserre F, Beuzelin D, Ducheix S, Huc L, Polizzi A, et al. Adverse effects  
648 of long-term exposure to bisphenol A during adulthood leading to hyperglycaemia and  
649 hypercholesterolemia in mice. *Toxicology.* 2014 Nov 5;325:133–43.
- 650 81. Kim MJ, Moon MK, Kang GH, Lee KJ, Choi SH, Lim S, et al. Chronic exposure to  
651 bisphenol A can accelerate atherosclerosis in high-fat-fed apolipoprotein E knockout  
652 mice. *Cardiovasc Toxicol.* 2014 Jun;14(2):120–8.

- 653 82. Ding S, Fan Y, Zhao N, Yang H, Ye X, He D, et al. High-fat diet aggravates glucose  
654 homeostasis disorder caused by chronic exposure to bisphenol A. *J Endocrinol*. 2014  
655 Apr;221(1):167–79.
- 656 83. Lai K-P, Chung Y-T, Li R, Wan H-T, Wong CK-C. Bisphenol A alters gut microbiome:  
657 Comparative metagenomics analysis. *Environ Pollut Barking Essex* 1987. 2016  
658 Nov;218:923–30.
- 659 84. Javurek AB, Spollen WG, Johnson SA, Bivens NJ, Bromert KH, Givan SA, et al. Effects  
660 of exposure to bisphenol A and ethinyl estradiol on the gut microbiota of parents and  
661 their offspring in a rodent model. *Gut Microbes*. 2016 Nov;7(6):471–85.
- 662 85. Koestel ZL, Backus RC, Tsuruta K, Spollen WG, Johnson SA, Javurek AB, et al.  
663 Bisphenol A (BPA) in the serum of pet dogs following short-term consumption of  
664 canned dog food and potential health consequences of exposure to BPA. *Sci Total*  
665 *Environ*. 2016 Dec 5;
- 666 86. Schroeder BO, Bäckhed F. Signals from the gut microbiota to distant organs in  
667 physiology and disease. *Nat Med*. 2016 Oct;22(10):1079–89.
- 668 87. Sonnenburg JL, Bäckhed F. Diet-microbiota interactions as moderators of human  
669 metabolism. *Nature*. 2016 Jul 6;535(7610):56–64.
- 670 88. Ashby J, Tinwell H, Haseman J. Lack of effects for low dose levels of bisphenol A and  
671 diethylstilbestrol on the prostate gland of CF1 mice exposed in utero. *Regul Toxicol*  
672 *Pharmacol RTP*. 1999 Oct;30(2 Pt 1):156–66.
- 673 89. Cagen SZ, Waechter JM, Dimond SS, Breslin WJ, Butala JH, Jekat FW, et al. Normal  
674 reproductive organ development in CF-1 mice following prenatal exposure to bisphenol  
675 A. *Toxicol Sci Off J Soc Toxicol*. 1999 Jul;50(1):36–44.
- 676 90. Cagen SZ, Waechter JM, Dimond SS, Breslin WJ, Butala JH, Jekat FW, et al. Normal  
677 reproductive organ development in Wistar rats exposed to bisphenol A in the drinking  
678 water. *Regul Toxicol Pharmacol RTP*. 1999 Oct;30(2 Pt 1):130–9.
- 679 91. Howdeshell KL, Saal FS vom. Developmental Exposure to Bisphenol A: Interaction  
680 with Endogenous Estradiol during Pregnancy in Mice. *Am Zool*. 2000;40(3):429–37.
- 681 92. Howdeshell KL, Hotchkiss AK, Thayer KA, Vandenberg JG, vom Saal FS.  
682 Environmental toxins: Exposure to bisphenol A advances puberty. *Nature*. 1999 Oct  
683 21;401(6755):763–4.
- 684 93. Rubin BS, Murray MK, Damassa DA, King JC, Soto AM. Perinatal exposure to low  
685 doses of bisphenol A affects body weight, patterns of estrous cyclicity, and plasma LH  
686 levels. *Environ Health Perspect*. 2001 Jul;109(7):675–80.
- 687 94. Honma S, Suzuki A, Buchanan DL, Katsu Y, Watanabe H, Iguchi T. Low dose effect of  
688 in utero exposure to bisphenol A and diethylstilbestrol on female mouse reproduction.  
689 *Reprod Toxicol Elmsford N*. 2002 Apr;16(2):117–22.
- 690 95. Nagao T, Saito Y, Usumi K, Yoshimura S, Ono H. Low-dose bisphenol A does not  
691 affect reproductive organs in estrogen-sensitive C57BL/6N mice exposed at the sexually

- 692 mature, juvenile, or embryonic stage. *Reprod Toxicol Elmsford N.* 2002 Apr;16(2):123–  
693 30.
- 694 96. Akingbemi BT, Sottas CM, Koulova AI, Klinefelter GR, Hardy MP. Inhibition of  
695 testicular steroidogenesis by the xenoestrogen bisphenol A is associated with reduced  
696 pituitary luteinizing hormone secretion and decreased steroidogenic enzyme gene  
697 expression in rat Leydig cells. *Endocrinology.* 2004 Feb;145(2):592–603.
- 698 97. Nikaido Y, Yoshizawa K, Danbara N, Tsujita-Kyutoku M, Yuri T, Uehara N, et al.  
699 Effects of maternal xenoestrogen exposure on development of the reproductive tract and  
700 mammary gland in female CD-1 mouse offspring. *Reprod Toxicol Elmsford N.* 2004  
701 Sep;18(6):803–11.
- 702 98. Miyawaki J, Sakayama K, Kato H, Yamamoto H, Masuno H. Perinatal and postnatal  
703 exposure to bisphenol a increases adipose tissue mass and serum cholesterol level in  
704 mice. *J Atheroscler Thromb.* 2007 Oct;14(5):245–52.
- 705 99. Howdeshell KL, Furr J, Lambright CR, Wilson VS, Ryan BC, Gray LE. Gestational and  
706 lactational exposure to ethinyl estradiol, but not bisphenol A, decreases androgen-  
707 dependent reproductive organ weights and epididymal sperm abundance in the male long  
708 evans hooded rat. *Toxicol Sci Off J Soc Toxicol.* 2008 Apr;102(2):371–82.
- 709 100. Somm E, Schwitzgebel VM, Toulotte A, Cederroth CR, Combescure C, Nef S, et al.  
710 Perinatal exposure to bisphenol a alters early adipogenesis in the rat. *Environ Health*  
711 *Perspect.* 2009 Oct;117(10):1549–55.
- 712 101. Alonso-Magdalena P, Vieira E, Soriano S, Menes L, Burks D, Quesada I, et al.  
713 Bisphenol A exposure during pregnancy disrupts glucose homeostasis in mothers and  
714 adult male offspring. *Environ Health Perspect.* 2010 Sep;118(9):1243–50.
- 715 102. Ryan KK, Haller AM, Sorrell JE, Woods SC, Jandacek RJ, Seeley RJ. Perinatal  
716 exposure to bisphenol-a and the development of metabolic syndrome in CD-1 mice.  
717 *Endocrinology.* 2010 Jun;151(6):2603–12.
- 718 103. Wei J, Lin Y, Li Y, Ying C, Chen J, Song L, et al. Perinatal exposure to bisphenol A at  
719 reference dose predisposes offspring to metabolic syndrome in adult rats on a high-fat  
720 diet. *Endocrinology.* 2011 Aug;152(8):3049–61.
- 721 104. Anderson OS, Peterson KE, Sanchez BN, Zhang Z, Mancuso P, Dolinoy DC. Perinatal  
722 bisphenol A exposure promotes hyperactivity, lean body composition, and hormonal  
723 responses across the murine life course. *FASEB J Off Publ Fed Am Soc Exp Biol.* 2013  
724 Apr;27(4):1784–92.
- 725 105. Angle BM, Do RP, Ponzi D, Stahlhut RW, Drury BE, Nagel SC, et al. Metabolic  
726 disruption in male mice due to fetal exposure to low but not high doses of bisphenol A  
727 (BPA): evidence for effects on body weight, food intake, adipocytes, leptin, adiponectin,  
728 insulin and glucose regulation. *Reprod Toxicol Elmsford N.* 2013 Dec;42:256–68.
- 729 106. Liu J, Yu P, Qian W, Li Y, Zhao J, Huan F, et al. Perinatal bisphenol A exposure and  
730 adult glucose homeostasis: identifying critical windows of exposure. *PloS One.*  
731 2013;8(5):e64143.

107. van Esterik JCJ, Dollé MET, Lamoree MH, van Leeuwen SPJ, Hamers T, Legler J, et al. Programming of metabolic effects in C57BL/6JxFVB mice by exposure to bisphenol A during gestation and lactation. *Toxicology*. 2014 Jul 3;321:40–52.
108. Johnson SA, Painter MS, Javurek AB, Ellersieck MR, Wiedmeyer CE, Thyfault JP, et al. Sex-dependent effects of developmental exposure to bisphenol A and ethinyl estradiol on metabolic parameters and voluntary physical activity. *J Dev Orig Health Dis*. 2015 Dec;6(6):539–52.
109. Rubin BS, Paranjpe M, DaFonte T, Schaeberle C, Soto AM, Obin M, et al. Perinatal BPA exposure alters body weight and composition in a dose specific and sex specific manner: The addition of peripubertal exposure exacerbates adverse effects in female mice. *Reprod Toxicol Elmsford N*. 2016 Aug 2;
110. García-Arévalo M, Alonso-Magdalena P, Servitja J-M, Boronat-Belda T, Merino B, Villar-Pazos S, et al. Maternal Exposure to Bisphenol-A During Pregnancy Increases Pancreatic  $\beta$ -Cell Growth During Early Life in Male Mice Offspring. *Endocrinology*. 2016 Sep 13;157(11):4158–71.
111. Gao L, Wang HN, Zhang L, Peng FY, Jia Y, Wei W, et al. Effect of Perinatal Bisphenol A Exposure on Serum Lipids and Lipid Enzymes in Offspring Rats of Different Sex. *Biomed Environ Sci BES*. 2016 Sep;29(9):686–9.
112. Thigpen JE, Setchell KDR, Kissling GE, Locklear J, Caviness GF, Whiteside T, et al. The estrogenic content of rodent diets, bedding, cages, and water bottles and its effect on bisphenol A studies. *J Am Assoc Lab Anim Sci JAALAS*. 2013 Mar;52(2):130–41.
113. Howdeshell KL, Peterman PH, Judy BM, Taylor JA, Orazio CE, Ruhlen RL, et al. Bisphenol A is released from used polycarbonate animal cages into water at room temperature. *Environ Health Perspect*. 2003 Jul;111(9):1180–7.
114. Azzouz A, Ballesteros E. Trace analysis of endocrine disrupting compounds in environmental water samples by use of solid-phase extraction and gas chromatography with mass spectrometry detection. *J Chromatogr A*. 2014 Sep 19;1360:248–57.
115. Luo L, Liu M. Adipose tissue in control of metabolism. *J Endocrinol*. 2016 Jan 12;231(3):R77–99.
116. Friedman JM, Halaas JL. Leptin and the regulation of body weight in mammals. *Nature*. 1998 Oct 22;395(6704):763–70.
117. Ahima RS, Flier JS. Leptin. *Annu Rev Physiol*. 2000;62:413–37.
118. Maffei M, Halaas J, Ravussin E, Pratley RE, Lee GH, Zhang Y, et al. Leptin levels in human and rodent: measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. *Nat Med*. 1995 Nov;1(11):1155–61.
119. Porreca I, Ulloa-Severino L, Almeida P, Cuomo D, Nardone A, Falco G, et al. Molecular targets of developmental exposure to bisphenol A in diabetes: a focus on endoderm-derived organs. *Obes Rev Off J Int Assoc Study Obes*. 2017 Jan;18(1):99–108.

- 770 120. Masuno H, Kidani T, Sekiya K, Sakayama K, Shiosaka T, Yamamoto H, et al. Bisphenol  
771 A in combination with insulin can accelerate the conversion of 3T3-L1 fibroblasts to  
772 adipocytes. *J Lipid Res.* 2002 May;43(5):676–84.
- 773 121. Ohlstein JF, Strong AL, McLachlan JA, Gimble JM, Burow ME, Bunnell BA. Bisphenol  
774 A enhances adipogenic differentiation of human adipose stromal/stem cells. *J Mol*  
775 *Endocrinol.* 2014 Dec;53(3):345–53.
- 776 122. Valentino R, D’Esposito V, Passaretti F, Liotti A, Cabaro S, Longo M, et al. Bisphenol-  
777 A impairs insulin action and up-regulates inflammatory pathways in human  
778 subcutaneous adipocytes and 3T3-L1 cells. *PloS One.* 2013;8(12):e82099.
- 779 123. Dai Y-E, Chen W, Qi H, Liu Q-Q. Effect of bisphenol A on SOCS-3 and insulin  
780 signaling transduction in 3T3-L1 adipocytes. *Mol Med Rep.* 2016 Jul 1;14(1):331–6.
- 781 124. Ariemma F, D’Esposito V, Liguoro D, Oriente F, Cabaro S, Liotti A, et al. Low-Dose  
782 Bisphenol-A Impairs Adipogenesis and Generates Dysfunctional 3T3-L1 Adipocytes.  
783 *PloS One.* 2016;11(3):e0150762.
- 784 125. Wetherill YB, Akingbemi BT, Kanno J, McLachlan JA, Nadal A, Sonnenschein C, et al.  
785 In vitro molecular mechanisms of bisphenol A action. *Reprod Toxicol Elmsford N.* 2007  
786 Sep;24(2):178–98.
- 787 126. Boucher JG, Husain M, Rowan-Carroll A, Williams A, Yauk CL, Atlas E. Identification  
788 of mechanisms of action of bisphenol a-induced human preadipocyte differentiation by  
789 transcriptional profiling. *Obes Silver Spring Md.* 2014 Nov;22(11):2333–43.
- 790 127. Boucher JG, Boudreau A, Atlas E. Bisphenol A induces differentiation of human  
791 preadipocytes in the absence of glucocorticoid and is inhibited by an estrogen-receptor  
792 antagonist. *Nutr Diabetes.* 2014 Jan 13;4:e102.
- 793 128. Atlas E, Pope L, Wade MG, Kawata A, Boudreau A, Boucher JG. Bisphenol A increases  
794 aP2 expression in 3T3L1 by enhancing the transcriptional activity of nuclear receptors at  
795 the promoter. *Adipocyte.* 2014 Jul 1;3(3):170–9.
- 796 129. Ahmed S, Atlas E. Bisphenol S- and bisphenol A-induced adipogenesis of murine  
797 preadipocytes occurs through direct peroxisome proliferator-activated receptor gamma  
798 activation. *Int J Obes* 2005. 2016 Oct;40(10):1566–73.
- 799 130. Ben-Jonathan N, Steinmetz R. Xenoestrogens: the emerging story of bisphenol a. *Trends*  
800 *Endocrinol Metab TEM.* 1998 Apr;9(3):124–8.
- 801 131. Lu C, Cheng S-Y. Thyroid hormone receptors regulate adipogenesis and carcinogenesis  
802 via crosstalk signaling with peroxisome proliferator-activated receptors. *J Mol*  
803 *Endocrinol.* 2010 Mar;44(3):143–54.
- 804 132. Sargis RM, Johnson DN, Choudhury RA, Brady MJ. Environmental endocrine  
805 disruptors promote adipogenesis in the 3T3-L1 cell line through glucocorticoid receptor  
806 activation. *Obes Silver Spring Md.* 2010 Jul;18(7):1283–8.



- 807 133. Williams G. Aromatase up-regulation, insulin and raised intracellular oestrogens in men,  
808 induce adiposity, metabolic syndrome and prostate disease, via aberrant ER- $\alpha$  and GPER  
809 signalling. *Mol Cell Endocrinol.* 2012 Apr 4;351(2):269–78.
- 810 134. Ali AT, Hochfeld WE, Myburgh R, Pepper MS. Adipocyte and adipogenesis. *Eur J Cell*  
811 *Biol.* 2013 Jul;92(6–7):229–36.
- 812 135. Kidani T, Kamei S, Miyawaki J, Aizawa J, Sakayama K, Masuno H. Bisphenol A  
813 downregulates Akt signaling and inhibits adiponectin production and secretion in 3T3-  
814 L1 adipocytes. *J Atheroscler Thromb.* 2010 Aug 31;17(8):834–43.
- 815 136. Hart RJ. Physiological Aspects of Female Fertility: Role of the Environment, Modern  
816 Lifestyle, and Genetics. *Physiol Rev.* 2016 Jul 1;96(3):873–909.
- 817 137. Deb P, Bhan A, Hussain I, Ansari KI, Bobzean SA, Pandita TK, et al. Endocrine  
818 disrupting chemical, bisphenol-A, induces breast cancer associated gene HOXB9  
819 expression in vitro and in vivo. *Gene.* 2016 Sep 30;590(2):234–43.
- 820 138. Frayling TM, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, Lindgren CM, et al. A  
821 common variant in the FTO gene is associated with body mass index and predisposes to  
822 childhood and adult obesity. *Science.* 2007 May 11;316(5826):889–94.
- 823 139. Scuteri A, Sanna S, Chen W-M, Uda M, Albai G, Strait J, et al. Genome-Wide  
824 Association Scan Shows Genetic Variants in the FTO Gene Are Associated with  
825 Obesity-Related Traits. *PLOS Genet.* 2007 jul;3(7):e115.
- 826 140. Singh RK, Kumar P, Mahalingam K. Molecular genetics of human obesity: A  
827 comprehensive review. *C R Biol.* 2017 Jan 12;
- 828 141. Hindorff LA, Sethupathy P, Junkins HA, Ramos EM, Mehta JP, Collins FS, et al.  
829 Potential etiologic and functional implications of genome-wide association loci for  
830 human diseases and traits. *Proc Natl Acad Sci U S A.* 2009 Jun 9;106(23):9362–7.
- 831 142. Goldberg AD, Allis CD, Bernstein E. Epigenetics: a landscape takes shape. *Cell.* 2007  
832 Feb 23;128(4):635–8.
- 833 143. Desai M, Jellyman JK, Ross MG. Epigenomics, gestational programming and risk of  
834 metabolic syndrome. *Int J Obes* 2005. 2015 Apr;39(4):633–41.
- 835 144. Doshi T, Mehta SS, Dighe V, Balasinor N, Vanage G. Hypermethylation of estrogen  
836 receptor promoter region in adult testis of rats exposed neonatally to bisphenol A.  
837 *Toxicology.* 2011 Nov 18;289(2–3):74–82.
- 838 145. Dolinoy DC, Huang D, Jirtle RL. Maternal nutrient supplementation counteracts  
839 bisphenol A-induced DNA hypomethylation in early development. *Proc Natl Acad Sci.*  
840 2007 Jul 8;104(32):13056–61.
- 841 146. Warita K, Mitsuhashi T, Ohta K, Suzuki S, Hoshi N, Miki T, et al. Gene expression of  
842 epigenetic regulatory factors related to primary silencing mechanism is less susceptible  
843 to lower doses of bisphenol A in embryonic hypothalamic cells. *J Toxicol Sci.*  
844 2013;38(2):285–9.

- 845 147. Ross MG, Desai M. Developmental Programming of Offspring Obesity, Adipogenesis,  
846 and Appetite. *Clin Obstet Gynecol*. 2013 Sep;56(3):529.
- 847 148. Rosenmai AK, Dybdahl M, Pedersen M, Alice van Vugt-Lussenburg BM, Wedebye EB,  
848 Taxvig C, et al. Are structural analogues to bisphenol a safe alternatives? *Toxicol Sci*  
849 *Off J Soc Toxicol*. 2014 May;139(1):35–47.
- 850 149. Grignard E, Lapenna S, Bremer S. Weak estrogenic transcriptional activities of  
851 Bisphenol A and Bisphenol S. *Toxicol Vitro Int J Publ Assoc BIBRA*. 2012  
852 Aug;26(5):727–31.
- 853 150. Liu J, Li J, Wu Y, Zhao Y, Luo F, Li S, et al. Bisphenol A Metabolites and Bisphenol S  
854 in Paired Maternal and Cord Serum. *Environ Sci Technol*. 2017 Feb 6;
- 855 151. Rochester JR, Bolden AL. Bisphenol S and F: A Systematic Review and Comparison of  
856 the Hormonal Activity of Bisphenol A Substitutes. *Environ Health Perspect*. 2015  
857 Jul;123(7):643–50.
- 858 152. Pivnenko K, Pedersen GA, Eriksson E, Astrup TF. Bisphenol A and its structural  
859 analogues in household waste paper. *Waste Manag*. 2015 Oct;44:39–47.
- 860 153. Ivry Del Moral L, Le Corre L, Poirier H, Niot I, Truntzer T, Merlin J-F, et al. Obesogen  
861 effects after perinatal exposure of 4,4'-sulfonyldiphenol (Bisphenol S) in C57BL/6 mice.  
862 *Toxicology*. 2016 May 16;357–358:11–20.
- 863 154. Héliès-Toussaint C, Peyre L, Costanzo C, Chagnon M-C, Rahmani R. Is bisphenol S a  
864 safe substitute for bisphenol A in terms of metabolic function? An in vitro study. *Toxicol*  
865 *Appl Pharmacol*. 2014 Oct 15;280(2):224–35.
- 866 155. Heindel JJ, Newbold R, Schug TT. Endocrine disruptors and obesity. *Nat Rev*  
867 *Endocrinol*. 2015 Nov;11(11):653–61.
- 868 156. Heindel JJ, Schug TT. The Perfect Storm for Obesity. *Obesity*. 2013 Jun 1;21(6):1079–  
869 80.
- 870