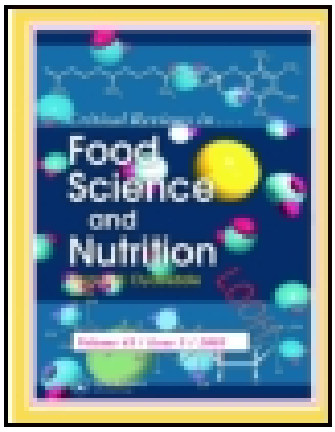


Critical Reviews in Food Science and Nutrition
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/bfsn20

# BPA, an Energy Balance Disruptor

L. Le Corre [a] , P. Besnard [a] & M.-C. Chagnon [a]
[a] Derttech Packtox, University of Burgundy , INSERM U866, NUTOX, Dijon , France
Accepted author version posted online: 20 Sep 2013.

To cite this article: L. Le Corre , P. Besnard & M.-C. Chagnon (2013): BPA, an Energy Balance Disruptor, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2012.678421

To link to this article: http://dx.doi.org/10.1080/10408398.2012.678421

# BPA, an Energy Balance Disruptor

Le Corre L.*, Besnard P. , Chagnon M.-C.

INSERM U866, NUTOX, Derttech Packtox, University of Burgundy, Dijon, France



**ABSTRACT**:

Bisphenol A (BPA) is used extensively in the world and is present in a diverse range of manufactured articles including dental resins, polycarbonate plastics and the inner coating of food cans. It is a high volume chemical, with global production at 3.6 $10^9$ kg per year. BPA was identified as a high priority for assessment of human health risk because it was considered to present greatest potential for human exposure. Most studies of the health effects of BPA have focused on endocrine disruption leading to reproductive toxicity, but it displays additional side effects, including liver damage, disrupted pancreatic β-cell function, thyroid hormone disruption, and obesity-promoting effects. In this article, we reviewed specifically on the effects of BPA in energy balance.

Keywords: Bisphenol A, lipid and glucose homeostasis, endocrine disruptor, obesogens, toxic chemical.

*Corresponding author. Laboratoire de Toxicologie Alimentaire – Derttech Packtox - AgrosupDijon Nord – 1 Esplanade Erasme – 21000 Dijon – France. Tel.: +33 3 80 39 66 43; fax: +33 3 80 39 66 41. E-mail: l.le-corre@agrosupdijon.fr

 

## 1. Introduction

In 2002, Baillie-Hamilton reported that the obesity epidemic matches the significant increase of the use and distribution of industrial chemicals that may be playing a role in generation of obesity. The authors summarized data showing that the current obesity epidemic cannot be explained exclusively by changes in lifestyle. Chemical agents such as pesticides, organophosphates, polychlorinated biphenyls, polybrominated biphenyls, phthalates, BPA, heavy metals and solvents caused weight increase likely by interfering with weight homeostasis such as alterations in weight-controlling hormones, altered sensitivity to neurotransmitters or altered activity of the sympathetic nervous system (Baillie-Hamilton, 2002, Trasande, et al., 2008).

Among these environmental contaminants, BPA is currently the centre of attention for the scientists, media, public and governments. It is produce in a high volume in the worldwide and is used to manufacture i) polycarbonate plastic for food packaging and manufacturing products as plastic bottles and baby bottles ii) epoxyresin that lines most food and beverage cans and dental sealants. BPA is present in the environment as a result of direct releases from manufacturing or processing facilities, fugitive emission during processing and handling, or release of unreacted monomer from products. In 2006, EFSA considered that the overall oral No-Observed Effect Level (NOEL) for BPA was 5 mg/kg/day in rat and determined a tolerable daily intake of 0.05 mg/kg/day (EFSA, 2006). Many studies in human population report measurable BPA levels: 0.2 to 20 ng/ml in serum from both men and women from several countries and at different ages (Fung, et al., 2000, Inoue, et al., 2000, Takeuchi and Tsutsumi, 2002, Vandenberg, et al., 2007), 0.3 to 18.9 ng/mL in maternal plasma, 0.2 to 9.2 ng/mL in foetal plasma with BPA

concentrations higher in men than in women fetuses, and 1.0 to 104.9 ng/g in placental tissue. These results indicate that BPA crosses the maternal foetal placental barrier. (Schonfelder, et al., 2002). Interestingly, BPA has also been shown to accumulate in fat, with detectable levels in 50% of breast adipose tissue samples from women (Fernandez, et al., 2007).

Most studies of the health effects of BPA have focused on well-documented estrogenic activity and reprotoxicity, but reports have highlighted additional side effects, including liver damage (Bindhumol, et al., 2003, Elsby, et al., 2001, Nakagawa and Tayama, 2000), promotion of oxidative stress and inflammation (Yang, et al., 2009), disrupted pancreatic β-cell function (Ropero, et al., 2008), thyroid hormone disruption (Moriyama, et al., 2002), decrease of intestinal function (Braniste, et al., 2010) and obesity-promoting effects.

In this review, we summarize the impact of BPA on the energy balance and its mechanisms of action.

**2. Bisphenol A and energy homeostasis**

Without regards to the design features of studies, we can observe that BPA exposure could induce a gain of body weight and an alteration of plasma triacylglycerol (TG), total cholesterol (TC) and glucose levels. However, differences occurring in protocols induce inconsistent results. From this perspective, we performed an overview of articles in this issue with regards to major factors involved in activity of endocrine disruptor chemicals (EDC) as exposure windows, effects dependent of doses, administration route, species and gender.

### 2.1. Exposure windows

Currently available literature reveals an increase of body weight in offspring of dams exposed to BPA during gestation or even up to early postnatal period. It is now well established that foetus and newborn developments are particularly sensitive to EDC exposure which can induce adulthood harmful consequences (Gluckman and Hanson, 2004). The reprotoxic effect of diethylstilbestrol (DES) is one of the best examples of health consequence induced by a gestational exposure (Anderson, et al., 2000). Several physiological factors are responsible. As reported above, EDCs like BPA can cross the maternal foetal placental barrier and reach the foetus (Balakrishnan, et al., 2010, Schonfelder, et al., 2002). The perinatal period is characterized by hormone regulation of cell proliferation, migration and differentiation in developing organs. Moreover, during this stage, the organism has immature DNA repair mechanisms, immune system, detoxification and hepatic metabolism. Thus, it is not surprising that BPA effect on body weight gain occurs after exposure during foetal development.

The effects of BPA appear to be not dependent of the beginning and length of treatment. As reported, effects of BPA can occur after an exposure from GD6-GD15 up to the birth or not. As described by Howdeshell et al. (1999) and Nikaido et al. (2004), a gain of body weight can be observed in offspring from BPA-treated dams only before delivery (Howdeshell, et al., 1999, Nikaido, et al., 2004). Likewise, Rubin et al. (2001) shown that the effect of BPA on body weight increase were observed during the period of exposure, and persisted when BPA administration ceased (Rubin, et al., 2001).



 

**2.2. Dose effects of BPA**

Another key concept in the field of endocrine disruption is the existence of non-traditional dose response curves. Many EDCs and hormones exhibit response neither as the threshold nor as the linear nonthreshold common models. These U-shaped and inverted U-shaped dose response curves are considered “nonmonotonic” and are used as evidence that very low doses can be biologically efficient (Calabrese and Baldwin, 2001). These non-monotonic dose responses make difficult to predict responses in the low dose environmental exposure range based on exposures in the high dose range (Conolly and Lutz, 2004). These concepts are now well accepted for hormones and neurotransmitters but they are still not clearly admitted for endocrine disruptor. Concerning BPA, it exhibits generally a nonmonotonic inverted U-shaped dose response (Vandenberg, et al., 2009).

Rubin et al. (2001) performed an oral BPA exposure (0.1 mg (low dose) or 1.2 mg BPA/kg bw/day (high dose) in drinking water) on pregnant Sprague-Dawley rat to GD6 up to the weaning. They observed a significant increase (≥10%) of body weight of the pups born to BPA-treated females. Interestingly, animals exposed to low dose of BPA were heavier than those exposed to the high dose of BPA, which are consistent with a non-monotonic inverted-U-shaped BPA dose-response (Rubin, et al., 2001). In another study, Miyawaki et al. (2007) exposed pregnant mice to oral administration of BPA in drinking water (~0.3 and ~3 mg/kg/day) from GD10 up to PND30 of pups. Body weight of offspring was significantly increased and exhibited a positive correlation with adipose mass. However, there was a sex effect as BPA induced a non-monotonic and inverted-U-shape dose-response increase in the mean adipose tissue mass in

female offspring, while it caused a monotonic dose-response increase in this mass in male offspring. In the same study, the authors described an increase of plasma TC and TG levels which displayed a non-monotonic and inverted-U-shaped dose-response in female as well as male mice (Miyawaki, et al., 2007). More recently, Alonso-Magdalena et al. (2010) shown that administration of 10 and 100 µg/kg/day of BPA (subcutaneously injected) to pregnant OF-1 mice was associated with higher birth weight up to the weaning but only with the exposure to 10µg/kg/day BPA (Alonso-Magdalena, et al., 2010). Likewise, Wei et al. (2011) studied effects of perinatal exposure to 50, 250 and 1250 µg/kg bw/d in Wistar rats on a normal and high-fat diet. They observed that only 50 µg/kg bw/d of BPA resulted in increased body weight, elevated serum insulin, and impaired glucose tolerance in adult offspring. On a high-fat diet, such detrimental effects were accelerated and exacerbated. No adverse effect of perinatal BPA exposure at 250 and1250 µg/kg bw/d was observed (Wei, et al., 2011).

Concerning glucose homeostasis, Alonso-Magdalena et al. (2010) shown that administration of 10 and 100 µg/kg of BPA (subcutaneously injected twice per day) to adult male mice produced a rapid increase in plasma insulin and a decrease in blood glucose after only 30 min. These alterations occurred according to an inverted-U shape dose-response curve (Alonso-Magdalena, et al., 2008).



### 2.3. Species and gender dependent effects of BPA

Concerning the species dependent effect, the major studies were performed in mice and rat model. The lack of data doesn't permit to clearly conclude on this issue. However, it is well

known that in human xenobiotics are better metabolized and eliminated than in murine models. This fact must be considered before conclude to the potential effect of BPA notably.

As above described, Miyawaki et al. (2007) reported an effect of BPA which was different according mouse offspring gender (cf. dose effects of BPA). Moreover, TC level increase was more significant in females with a positive correlation with adipose tissue weight. Whereas in males, TG level increase was more significant with a negative correlation with adipose tissue weight but a positive correlation with non-esterified fatty acid serum level. Thus, it seems that BPA induce hypercholesterolemia in female offspring and hypertriglyceridemia in male offspring. In the same study, plasma leptin level was increased only in female offspring (Miyawaki, et al., 2007).

Likewise, in a recent study, Sprague Dawley rats treated with drinking water containing 1 mg/L BPA from GD6 through the end of lactation showed a weight increase of male and female pups on PND1. However, on PND21, body weight was increased only in females in correlation with parametrial white adipose tissue (pWAT) weight (Somm, et al., 2009).



**2.4. Impact of administration way**

The administration way determines the availability of compounds and consequently its activities in an organism. In studies using diet route or oral gavages, the authors failed to found an effect of BPA (Kwon, et al., 2000, Palanza, et al., 2002, Ryan, et al., 2010, Seidlova-Wuttke, et al., 2005) in opposition to BPA diluted in drinking water (Miyawaki, et al., 2007, Rubin, et al., 2001, Somm, et al., 2009) or subcutaneous injection (Alonso-Magdalena, et al., 2008, Nikaido, et al.,

2004). As an exception, an increased body weight was reported at the time of weaning in female CD-1 mice born to mothers that received an oral dose of 2 µg BPA/kg bw /day on gestational days 11–17. However, the difference in body weight was seen in females positioned between two females in the uterine horn during gestation. This finding suggests that the magnitude of BPA's effects on body weight were influenced by subtle differences in the hormone environment *in utero (Howdeshell, et al., 1999)*. As described above, Wei et al. (2011) also observed effects of a perinatal exposure to 50 µg/ kg bw/d of BPA administrated by oral gavage (Wei, et al., 2011).

Even if the exposure of BPA via drinking water or subcutaneous injection appears to be more efficient, there is no clear evidence to conclude of this issue. In all *in vivo* studies, the range of BPA doses used is large. Thus, the relationship between route of administration and dose-dependent effects of BPA is difficult to highlight. The understanding of current levels of human BPA exposure is complicated by the limited knowledge of the ways by which humans are exposed. Because BPA leaches into food from plastic packaging and resin linings of food and beverage containers, it has been widely assumed that the consumption of contaminated food and beverages represents the major route of human exposure. However, new sources of exposure continue to be uncovered, such as thermal (carbonless) receipts used for many daily transactions that contain a coating of high levels of free BPA, raising the possibility that dermal transport may also be a significant source of exposure (Biedermann, et al., 2010, Zalko, et al., 2011)). There is also significant leaching of BPA from children's books (Sajiki, et al., 2010).

Concerning oral route of administration, differential processing of high doses relative to low doses of BPA may contribute to the inverted-U-shaped non-monotonic dose-response curve that

has been earlier described for this molecule and other compounds (Kern, et al., 2003, vom Saal, et al., 1998, vom Saal, et al., 1997). Pottenger *et al.* also reported that a single oral administration of BPA (10 mg/kg or 100 mg/kg) resulted in the metabolization of BPA to the monoglucuronide conjugate, the major urinary metabolite of the compound. Thus, BPA plasma levels were lower and the period of time that detectable levels of BPA were present in the plasma was abbreviated. Their results demonstrated a route dependency of BPA bioavailability in rats, with oral administration resulting in the lowest bioavailability, and offer an explanation for the apparent route differences in effect observed for BPA (Pottenger, et al., 2000). These data suggest that the BPA biotransformation is an important parameter to take into account according to the exposition way.

Many studies have attempted to reported the inability to detect unconjugated serum BPA based on one experiment conducted with a limited sample size and a relatively insensitive assay (Volkel, et al., 2002) as an indication that all administered BPA is completely metabolized during its first pass through the liver. In contrast, Taylor et al. (2011) found in their study with rhesus monkeys do not support this conclusion and also conclude that the adult rhesus monkey is a valid model for predicting the serum levels of conjugated BPA after oral exposure in humans Likewise, BPA pharmacokinetics in women, female monkeys, and mice is very similar. The authors compared the approximately 2 ng/mL unconjugated serum BPA reported in multiple human studies with their study where they found unconjugated serum BPA concentration of 0.5 ng/mL in both monkeys and mice after a 400 μg/kg oral dose, They concluded that total daily human exposure occurs via multiple routes and is much higher than previously assumed (Taylor, et al., 2011).

### 2.5. Body weight gain or a faster rate of growth?

The body weight gain observed in studies seems to be not only related to an increase of adipose tissue mass. Recently, Ryan et al. (2010) tested the hypothesis that perinatal exposure to an ecologically relevant dose of BPA (0.25µg/kg bw/d in the diet) results in increased susceptibility to high-fat diet-induced obesity and glucose intolerance in adult CD-1 mice. They found that weaning mice exposed to BPA during gestation and lactation are heavier compared with control mice. They also observed that BPA-treated mice are longer than controls at 4 wk of age, but these differences are no longer apparent when the mice reach adulthood, even when tested on a high-fat diet. They conclude that this larger size-for-age represents a faster rate of growth early in development rather than an obese, diabetic phenotype in adulthood (Ryan, et al., 2010). In contrast, Miyawaki et al. (2007) showed that body weight of offspring was significantly increased with a positive correlation with adipose mass (Miyawaki, et al., 2007). In a recent study, Sprague Dawley rats treated with drinking water containing 1 mg/L BPA showed a weight increase of male and female pups. However, body weight was increased only in females in correlation with parametrial white adipose tissue (pWAT) weight. This excess of pWAT was associated with adipocyte hypertrophy and overexpression of lipogenic genes in adipocyte and liver (Somm, et al., 2009). Thus, activity of BPA seems to be both the consequence of growth stimulation and an increase of lipid storage.

### 2.6. Mechanism of Action

Potential targets of BPA activity could be the TC and TG content and the adipogenesis. As described above in studies performed in vivo, effects of BPA could be mediated by an alteration in TC and TG content. These results are in accordance with *in vitro* studies which reported an accumulation of TG in adipocyte and hepatocyte cells after BPA treatment (Masuno, et al., 2005, Masuno, et al., 2002, Wada, et al., 2007). In these studies, authors investigated the BPA-induced differentiation of preadipocytes (3T3-L1 mouse preadipocyte cell line) to mature adipocytes. Wada et al. (2007) described that 10μM BPA significantly stimulated the accumulation of TG in mature adipocytes. The authors concluded that BPA can promote the differentiation of preadipocytes to mature adipocytes. Likewise, they observed that BPA (10μM) also stimulate the lipid accumulation in human hepatocellular carcinoma cell line HuH-7. Furthermore, BPA (~80μM) in combination with insulin seems to be able to accelerate the conversion of 3T3-L1 to adipocytes. 3T3-L1 cells treated with BPA for 2 days and subsequently treated with insulin alone for 9 days exhibited an increase of 150% in the TG content. BPA resulted in the presence of larger lipid droplets in the differentiated cells. Insulin and BPA interacted synergistically to further accelerate these processes (Masuno, et al., 2005, Masuno, et al., 2002). In contrast, Phrakonkham et al. failed to observe an alteration in TG content in 3T3-L1 treated with 80 μM of BPA for 48h and up to 8 days after this induction (Phrakonkham, et al., 2008).

Lipid accumulation in adipocytes is notably regulated by leptin protein hormone which is produced by adipocytes and it plays a key role in regulating energy intake and energy expenditure, including appetite and metabolism (Ceddia, et al., 2002, Farooqi and O'Rahilly,

2009). Interestingly, in ovariectomized rats (3 months old), BPA (0.033 and 0.333 mg/kg/day) reduced serum leptin concentrations (Seidlova-Wuttke, et al., 2005). Miyawaki *et al.* (2007) had shown, *in vivo*, an increased of serum leptin level in female but no change in male. This augmentation was in positive correlation with adipose tissue weight, which is in agreement with actual knowledge since leptin is secreted in direct proportion to body adiposity (Woods and D'Alessio, 2008). Taken together, this discrepancy between effects of BPA on serum leptin level in ovariectomized rats in comparison with female mice and the no effect in male mice could be explained by the presence or not of endogen estrogens which alter the range of the inverted U-shaped dose-effect of BPA. In contrast, Phrakonkham et al. (2008) failed to obtain an alteration of leptin protein release in differentiated 3T3-L1 adipocytes treated by 80µM BPA although mRNA level was significantly increase (Phrakonkham, et al., 2008). Up-regulation of leptin mRNA level was also reported in 3T3-L1 treated 24h by 10 µM of BPA (Lee, et al., 2008).

Another adipocyte hormone, adiponectin seems to be a target of BPA effect. Adiponectin improves insulin sensitivity by increasing energy expenditure and fatty acid oxidation (Heidemann, et al., 2008). Low doses of BPA (0.1, 1, 10nM) inhibited adiponectin release from human breast, subcutaneous, and visceral adipose explants (Hugo, et al., 2008). In contrast, Wada et al. (2007) didn't show BPA (10µM) effect on adiponectin level secreted by 3T3-L1 preadipocytes (Wada *et al.*, 2007). This discrepancy must be explained due to the use of mature adipocytes in or preadipocytes, adiponectin expression has been found to be potently induced during adipocyte differentiation (Scherer, et al., 1995). It suggests that mature adipocytes in contrast to preadipocyte exhibit receptor or pathway which will be activated or inhibited by BPA.

Concerning glucose homeostasis, several studies investigated effects of BPA treatment in the rat pancreatic islets β cells after 1h as well as after 24h exposure. Thus, treatment with E2 (10μg/l) or BPA (10 and 100 μg/l) for 24 h induce significant increase of insulin secretion with 16.7 mM glucose, compared to the control. However, in contrast to E2, 1h BPA exposure did not significantly change the level of insulin release following glucose stimulation. In addition, exposure to 10 μg/l BPA (or E2) with transcription inhibitor Actinomycin D or pure anti-estrogen ICI 182,780 for 24 h significantly suppressed increase in insulin secretion. These results suggest that, similar to E2, 24h exposure to BPA induce insulin secretion *via* cytosolic/nuclear ERs (Adachi, et al., 2005). Likewise, Alonso-Magdalena et al. (2010) reported that long-term exposure to physiological levels of E2 (1nM) and environmentally relevant doses of BPA ((0.23 up to 22.83 μg/l (0.1 up to 100 nM)) increased β-cell insulin content, insulin gene expression and insulin release, yet pancreatic β-cell mass was unaltered. The pancreatic insulin content was up-regulated through a mechanism involving activation of ERα involving ERK1/2. Interestingly, BPA-induced increase of insulin content followed an inverted-U shape dose-response curve, being significant at doses as low as 100pM-1 nM and equally effective as E2 with 1 nM of BPA (Alonso-Magdalena, et al., 2008).

Likewise, in a recent report, Makaji et al. (2011) described that BPA treatment directly affected insulin secretion in mouse beta TC-6 cells. Furthermore, chronic exposure to BPA altered the expression of key proteins in the cellular and endoplasmic reticulum stress response. Authors suggest that long-term BPA exposure may be detrimental to β-cell function and ultimately be an important contributor to the etiology of Type 2 diabetes (Makaji, et al., 2011).

The glucose uptake is also important for its homeostasis. The transport of glucose over the plasma membrane is mediated by members of the glucose transporters (GLUT) family. *In vitro*, Sakurai *et al.* (2004) reported that BPA (1 and 100μM) stimulated insulin-dependent glucose uptake and increased expression of GLUT4 in 3T3-F442A murine pre-adipocytes whereas E2 and lower BPA levels (<1μM) were ineffective. Of interest, this effect of BPA was not inhibited by ICI 182,780, revealing that this effect is nuclear ER independent (Sakurai, et al., 2004).

Development and maturation of brain circuits involved in the regulation of food intake and metabolism occur during the perinatal period (Grove, et al., 2005, Simerly, 2008, Xiao, et al., 2007). They could be potential direct or indirect targets of BPA action during perinatal exposure. Several studies have confirmed the ability of BPA to affect the developing brain even at very low doses (Richter, et al., 2007).



### 2.7. Molecular mechanisms induced by BPA

#### 2.7.1. Target genes in 3T3-L1 preadipocytes

By using DNA microarray with RNA from 3T3-L1 preadipocytes, BPA was described to up-regulated gene expression involved in lipid metabolism, adipocyte differentiation, and inflammation. Notably, the up-regulation of hormone-sensitive lipase, phospholipase A2, and phospholipase C involved in lipid metabolism were reported. Likewise, up-regulation of CD36, a receptor for oxidized- or acetylated-LDL, adiponectin and TNF-α, an important adipocytokine to induce insulin resistance, were also observed (Wada, et al., 2007). In contrast, mRNA expression

of resistin, an adipokine known to link obesity to Type 2 diabetes in rodents (Steppan and Lazar, 2004), was not altered in 3T3-L1 cells treated by 10μM of BPA for 24h (Lee, et al., 2008).

### 2.7.2. BPA an activator of PI3K pathways

Phosphatidylinositol 3-kinase (PI3K) is essential for lipid accumulation in 3T3-L1 adipocytes as reported by using a PI3K inhibitor LY294002 (Xia and Serrero, 1999). Likewise, activated PI3K induced phosphorylation of AKT kinase which was found to result in spontaneous differentiation of fibroblast into adipocytes in association with lipid accumulation (Kohn, et al., 1996). Consequently, Masuno *et al.* (2005) described that LY294002 blocked completely TG accumulation and adipocyte differentiation provoked by BPA. Moreover, BPA was able to increase the level of phospho-AKT (Masuno, et al., 2005). Then, TG accumulation and adipocyte differentiation induced by BPA was mediated by the activation of PI3K and AKT kinase pathway.

### 2.7.3. BPA, an estrogenic compound

As described above, sex-dependent and dose-dependent differences in body weight in response to early postnatal exposure to BPA suggest that estrogenic properties of BPA may contribute to effects on body weight.

About the effects of BPA on lipid homeostasis, none studies investigated whether BPA activated ER or not. In contrast, in glucose homeostasis, BPA seems to act partially through ER

pathways (Adachi, et al., 2005, Alonso-Magdalena, et al., 2008) and another pathway was found to be dependent of ncmER as reported in pancreatic islet cells (Alonso-Magdalena, et al., 2005). Pancreatic cells secrete insulin according to ionic events which generate an oscillatory electrical activity that causes intracellular calcium concentration ($[Ca^{2+}]i$) to oscillate as well. The oscillatory $[Ca^{2+}]i$ pattern triggers a pulsatile insulin secretion. $[Ca^{2+}]i$ oscillations is regulated by E2 in α- and β-cells. In the glucagon-containing α-cells, E2 suppressed $[Ca^{2+}]i$ oscillations generated by low glucose, whereas in β-cells it potentiates calcium ion signals (Ropero, et al., 2002). Interestingly, the E2 effect is initiated after binding to the no-classical membranar estrogen receptor (ncmER; (Nadal, et al., 2000, Ropero, et al., 2002)). In mouse pancreatic α-cells within isolated and intact islets of Langerhans, BPA (1nM) inhibited low-glucose–induced [Ca2+]i oscillations and consequently decreased glucagon release. Moreover, similarly to E2, BPA seems to acts *via* the ncmER as shown by the no-effect of the anti-estrogen ICI 182,780. Another related finding is that in pancreatic cells, BPA stimulates phosphorylation and activation of the transcription factor CREB within a few minutes via a calcium-dependent mechanism that is activated by ncmER (Quesada, et al., 2002). CREB also plays an important role in adipocyte differentiation, and it is possible that the effects of BPA on adipocyte differentiation thus also involve rapid effects on CREB (Alonso-Magdalena, et al., 2005).

BPA appeared also to bind to ncmER inducing an activation cascade as follow: stimulation of nitric oxide synthase (NOS) which produces NO and activates soluble guanylate cyclase. The resulting increase of cGMP levels activates PKG, inducing alteration in ion channels and producing the abolishment of low-glucose–induced [Ca2+]i (Alonso-Magdalena, et al., 2005).

### 2.7.4. BPA activates nuclear receptor pathways?

The other possibility is that BPA binds to other nuclear receptors, such as human steroid and xenobiotic receptor (Takeshita *et al.*, 2001). Notably, BPA is an indirect agonist of RXR but it must be previously metabolized; however, the metabolite that is responsible for the inducing activity is unknown (Li *et al.*, 2008). BPA also induced an increase of RXRα and RXRβ mRNA expression in murine embryos (Nishizawa, et al., 2005). Moreover, although bisphenol A diglycidyl ether (BADGE) is a antagonist of PPARγ, no evidence was reported to determine an effect of BPA on PPARγ activity. However, BPA was found to be able to increase the mRNA expression of PPARγ in 3T3-L1 preadipocyte (Phrakonkham, et al., 2008). PPARγ/RXR signallings have been identified as major regulators of adipogenesis (Rangwala and Lazar, 2000). BPA seems also to bind to thyroid receptor (TR) and distinctly regulate the action of TR function, thyroid hormone system being important for biological functions such as growth, development and metabolism (Jung, et al., 2007). To date and our knowledge, among the others nuclear receptors involved in energetic metabolism, effects of BPA on activities of liver X receptor (LXR), farnesoid X receptor (FXR), retinoic acid receptor (RAR) and RXR were not investigated and thus, remains potential targets for BPA studies. However, recently, it was reported that BPA was able to promote adipogenesis through the activation of the glucocorticoid receptor (Sargis, et al., 2010).

The last identified member of the orphan estrogen-related receptor (ERR) family, ERRγ, has been found to bind BPA (Matsushima, et al., 2008, Okada, et al., 2008). The functions of ERRγ have not been clearly defined. ERRγ is present in adipose tissue and recent data suggests

that ERRγ as ERRα and ERRβ, plays an important role in the transcriptional control of energy homeostasis (Giguere, 2008). Further studies are necessary to determine whether BPA may exert effects on ERRγ and its target genes.

### 2.7.5. Epigenetic modifications



Epigenetics refers to DNA methylation and chromatin acetylation modifications that persist from one cell division to the next despite a lack of change in the underlying DNA sequence. Some epigenetic changes show transgenerational inheritance. Epigenetics play an important role in cellular differentiation, allowing distinct cell types to have specific characteristics despite sharing the same DNA sequence. Endocrine disruptors have recently been shown to promote an epigenetic transgenerational phenotype involving a number of disease states (Anway and Skinner, 2006). Studies have mainly focused on epigenetic changes in reproductive tract tissues. In a recent review, authors highlighted researches indicating a consequence of prenatal BPA exposure for brain, behavior, and immune outcomes and discuss evidences for the role of epigenetic pathways in shaping these developmental effects. They conclude that though there is emerging evidence supporting the role of epigenetic mechanisms in these BPA-induced effects, further studies are needed to examine the correlation between BPA-induced epigenetic alterations, changes in gene expression, and phenotypic outcomes (Kundakovic and Champagne, 2011). In this way, similar effects could possibly occur in other differentiating endocrine responsive tissues.

### 2.8. BPA, an endocrine disruptor

Interestingly, others EDCs induces similar effects that BPA on energy balance suggesting that the same pathways are involved. For example, diethylstilbestrol (DES) is a very potent xenoestrogen and it has often been used as a positive control in toxicology experiments evaluating endocrine disruptors. Prenatal exposure with low dose of DES (1µg/kg/day) did not alter birth weight but induce a significant increase in adult body weight in a positive correlation with adipose tissue mass (Newbold, et al., 2005). Like BPA, effects of DES differ according to the period of exposure and dose levels which follow a non-monotonic dose-response curve. In studies of pancreatic cells in both primary culture and *in vivo* suggest that 1nM of DES affect the normal physiology of the endocrine pancreas by suppressing, as BPA, low-glucose–induced intracellular calcium ion ([Ca2+]i) oscillations in α-cells, the signal that triggers glucagon secretion (Alonso-Magdalena, et al., 2005).

An organotin, tributyltin chloride (TBT) has been shown to disrupt normal development and homeostatic controls over adipogenesis and energy balance (Grun and Blumberg, 2006, Tabb and Blumberg, 2006). TBT stimulates adipocytes differentiation *in vitro* and increases lipid droplets accumulation in 3T3-L1 cells (Inadera and Shimomura, 2005). *In vivo* exposure to TBT increased body fat mass and was involved in obesity development (Grun and Blumberg, 2006).

*In vitro* study show that nonylphenol have the same effects that BPA on lipid content in 3T3-L1 pre-adipocyte and HuH-7 hepatocytes cells (Wada, et al., 2007). Likewise, long-term exposure to nonylphenol promotes *in vitro* insulin secretion from rat pancreatic islets via cytosolic/nuclear estrogen receptors (Adachi, et al., 2005).



 

Among the phtalates, mono-ethyl-hexyl phthalate (MEHP) and mono-benzyl phthalate (MBzP) was found to activate PPARγ and to be associated with adipocyte differentiation of 3T3-L1 cells (Feige, et al., 2007).

**2.9 BPA and human metabolic disorders: epidemiological studies**

Although there are a large number of in vitro and experimental animal studies concerning the role of BPA and other "obesogens" in obesity and other co-morbidities associated with metabolic syndrome, only a few epidemiologic studies have examined the possible role of BPA in the human obesity epidemic. In human and to our knowledge, only one recent study highlighted specifically a correlation between BPA urinary level and an increased prevalence of obesity, diabetes but also of cardiovascular disease and liver-enzyme abnormalities obesity. Thus, BPA concentration in subjects with body mass index recommended (18.5-24.9) were 3.91 ng/ml while as it was 6.93 ng/ml in obese II category (BMI>35). However, this relation could be explain by an increased of dietary weight intakes associated with obesity which result in higher intakes of BPA (Lang *et al.*, 2008). Likewise, in the InCHIANTI Adult Population Study performed by Galloway et al. (2010) in order to define the relationship between daily bisphenol A excretion and associations with sex hormone concentrations, authors found higher excretion rates among men, younger respondents, and those with increasing waist circumference and weight. But no associations with the Body Mass Index was found (Galloway, et al., 2010). Melzer et al. (2010) found that Higher BPA concentrations were associated with coronary heart disease and diabetes in a cross-sectional analysis of US national health and nutrition examination survey (NHANES) data (Melzer, et al., 2010).

**3. Conclusions and Remarks**

Like others EDCs, BPA seems to be able to alter energy balance at different levels. Like DES, which is a strong agonist to estrogen receptor, BPA induce an increase of body weight. It may suggest that estrogen receptor pathway is preferentially activated by DES and BPA inducing an alteration of energy. Interestingly, it appears important to have an impregnation of BPA during the gestation period to observe significant effects. Like observed in endocrine disruption studies, BPA exhibit currently a non-monotonic inverted-U-shaped dose-response and a gender-response. It could be explained by both estrogenic and anti-androgenic effects of BPA. However, others pathways were involved (ncmER, PI3K/AKT) but it remains to made further studies to conclude. Another important parameter to evaluate is the administration way of BPA which interfere on its bioavalabilities and consequently its activities. In further study, the impact of new sources of BPA exposure (dermal, inhalation) should be investigated in order to consider the adverse effects of BPA in its enterity.

The alterations induced by BPA could expect that a chronic exposure lead to insulin resistance, energetic imbalance and subsequently could increase the incidence of obesity and/or diabetes. Certainly, additional studies are necessary to investigate the effects of BPA on metabolism disorder in order to define whether this is a compound-specific effect or a general effect of endocrine disruptor.

## 4. References

Adachi, T., Yasuda, K., Mori, C., Yoshinaga, M., Aoki, N., Tsujimoto, G. and Tsuda, K. (2005). Promoting insulin secretion in pancreatic islets by means of bisphenol A and nonylphenol via intracellular estrogen receptors. *Food Chem Toxicol*. **43**: 713-719.

Alonso-Magdalena, P., Laribi, O., Ropero, A. B., Fuentes, E., Ripoll, C., Soria, B. and Nadal, A. (2005). Low doses of bisphenol A and diethylstilbestrol impair Ca2+ signals in pancreatic alpha-cells through a nonclassical membrane estrogen receptor within intact islets of Langerhans. *Environ Health Perspect*. **113**: 969-977.

Alonso-Magdalena, P., Ropero, A. B., Carrera, M. P., Cederroth, C. R., Baquie, M., Gauthier, B. R., Nef, S., Stefani, E. and Nadal, A. (2008). Pancreatic insulin content regulation by the estrogen receptor ER alpha. *PLoS One*. **3**: e2069.

Alonso-Magdalena, P., Vieira, E., Soriano, S., Menes, L., Burks, D., Quesada, I. and Nadal, A. (2010). Bisphenol A exposure during pregnancy disrupts glucose homeostasis in mothers and adult male offspring. *Environ Health Perspect*. **118**: 1243-1250.

Anderson, L. M., Diwan, B. A., Fear, N. T. and Roman, E. (2000). Critical windows of exposure for children's health: cancer in human epidemiological studies and neoplasms in experimental animal models. *Environ Health Perspect*. **108 Suppl 3**: 573-594.

Anway, M. D. and Skinner, M. K. (2006). Epigenetic transgenerational actions of endocrine disruptors. *Endocrinology*. **147**: S43-49.

Baillie-Hamilton, P. F. (2002). Chemical toxins: a hypothesis to explain the global obesity epidemic. *J Altern Complement Med*. **8**: 185-192.



 

Balakrishnan, B., Henare, K., Thorstensen, E. B., Ponnampalam, A. P. and Mitchell, M. D. (2010). Transfer of bisphenol A across the human placenta. *Am J Obstet Gynecol*. **202**: 393 e391-397.

Biedermann, S., Tschudin, P. and Grob, K. (2010). Transfer of bisphenol A from thermal printer paper to the skin. *Anal Bioanal Chem*. **398**: 571-576.

Bindhumol, V., Chitra, K. C. and Mathur, P. P. (2003). Bisphenol A induces reactive oxygen species generation in the liver of male rats. *Toxicology*. **188**: 117-124.

Braniste, V., Jouault, A., Gaultier, E., Polizzi, A., Buisson-Brenac, C., Leveque, M., Martin, P. G., Theodorou, V., Fioramonti, J. and Houdeau, E. (2010). Impact of oral bisphenol A at reference doses on intestinal barrier function and sex differences after perinatal exposure in rats. *Proc Natl Acad Sci U S A*. **107**: 448-453.

Calabrese, E. J. and Baldwin, L. A. (2001). The frequency of U-shaped dose responses in the toxicological literature. *Toxicol Sci*. **62**: 330-338.

Ceddia, R. B., Koistinen, H. A., Zierath, J. R. and Sweeney, G. (2002). Analysis of paradoxical observations on the association between leptin and insulin resistance. *FASEB J*. **16**: 1163-1176.

Conolly, R. B. and Lutz, W. K. (2004). Nonmonotonic dose-response relationships: mechanistic basis, kinetic modeling, and implications for risk assessment. *Toxicol Sci*. **77**: 151-157.

EFSA (2006). Opinion of the scientific panelon food additives, flavourings, processing aids and materials in contact with food on a request from the Comission related to 2,2-bis(4-hydroxyphenyl)propane (Bisphenol A): Question number EFSA-Q-2005-100 adopted on 29 november 2006. *The EFSA journal*. **428**:

Elsby, R., Maggs, J. L., Ashby, J. and Park, B. K. (2001). Comparison of the modulatory effects of human and rat liver microsomal metabolism on the estrogenicity of bisphenol A: implications for extrapolation to humans. *J Pharmacol Exp Ther*. **297**: 103-113.

Farooqi, I. S. and O'Rahilly, S. (2009). Leptin: a pivotal regulator of human energy homeostasis. *Am J Clin Nutr*. **89**: 980S-984S.

Feige, J. N., Gelman, L., Rossi, D., Zoete, V., Metivier, R., Tudor, C., Anghel, S. I., Grosdidier, A., Lathion, C., Engelborghs, Y., Michielin, O., Wahli, W. and Desvergne, B. (2007). The endocrine disruptor monoethyl-hexyl-phthalate is a selective peroxisome proliferator-activated receptor gamma modulator that promotes adipogenesis. *J Biol Chem*. **282**: 19152-19166.

Fernandez, M. F., Arrebola, J. P., Taoufiki, J., Navalon, A., Ballesteros, O., Pulgar, R., Vilchez, J. L. and Olea, N. (2007). Bisphenol-A and chlorinated derivatives in adipose tissue of women. *Reprod Toxicol*. **24**: 259-264.

Fung, E. Y., Ewoldsen, N. O., St Germain, H. A., Jr., Marx, D. B., Miaw, C. L., Siew, C., Chou, H. N., Gruninger, S. E. and Meyer, D. M. (2000). Pharmacokinetics of bisphenol A released from a dental sealant. *J Am Dent Assoc*. **131**: 51-58.

Galloway, T., Cipelli, R., Guralnik, J., Ferrucci, L., Bandinelli, S., Corsi, A. M., Money, C., McCormack, P. and Melzer, D. (2010). Daily bisphenol A excretion and associations with sex hormone concentrations: results from the InCHIANTI adult population study. *Environ Health Perspect*. **118**: 1603-1608.

Giguere, V. (2008). Transcriptional control of energy homeostasis by the estrogen-related receptors. *Endocr Rev*. **29**: 677-696.

Gluckman, P. D. and Hanson, M. A. (2004). The developmental origins of the metabolic syndrome. *Trends Endocrinol Metab*. **15**: 183-187.

Grove, K. L., Grayson, B. E., Glavas, M. M., Xiao, X. Q. and Smith, M. S. (2005). Development of metabolic systems. *Physiol Behav*. **86**: 646-660.

Grun, F. and Blumberg, B. (2006). Environmental obesogens: organotins and endocrine disruption via nuclear receptor signaling. *Endocrinology*. **147**: S50-55.

Heidemann, C., Sun, Q., van Dam, R. M., Meigs, J. B., Zhang, C., Tworoger, S. S., Mantzoros, C. S. and Hu, F. B. (2008). Total and high-molecular-weight adiponectin and resistin in relation to the risk for type 2 diabetes in women. *Ann Intern Med*. **149**: 307-316.

Howdeshell, K. L., Hotchkiss, A. K., Thayer, K. A., Vandenbergh, J. G. and vom Saal, F. S. (1999). Exposure to bisphenol A advances puberty. *Nature*. **401**: 763-764.

Hugo, E. R., Brandebourg, T. D., Woo, J. G., Loftus, J., Alexander, J. W. and Ben-Jonathan, N. (2008). Bisphenol A at environmentally relevant doses inhibits adiponectin release from human adipose tissue explants and adipocytes. *Environ Health Perspect*. **116**: 1642-1647.

Inadera, H. and Shimomura, A. (2005). Environmental chemical tributyltin augments adipocyte differentiation. *Toxicol Lett*. **159**: 226-234.

Inoue, K., Kato, K., Yoshimura, Y., Makino, T. and Nakazawa, H. (2000). Determination of bisphenol A in human serum by high-performance liquid chromatography with multi-electrode electrochemical detection. *J Chromatogr B Biomed Sci Appl*. **749**: 17-23.

Jung, K. K., Kim, S. Y., Kim, T. G., Kang, J. H., Kang, S. Y., Cho, J. Y. and Kim, S. H. (2007). Differential regulation of thyroid hormone receptor-mediated function by endocrine disruptors. *Arch Pharm Res*. **30**: 616-623.

Kern, P. A., Di Gregorio, G. B., Lu, T., Rassouli, N. and Ranganathan, G. (2003). Adiponectin expression from human adipose tissue: relation to obesity, insulin resistance, and tumor necrosis factor-alpha expression. *Diabetes*. **52**: 1779-1785.

Kohn, A. D., Summers, S. A., Birnbaum, M. J. and Roth, R. A. (1996). Expression of a constitutively active Akt Ser/Thr kinase in 3T3-L1 adipocytes stimulates glucose uptake and glucose transporter 4 translocation. *J Biol Chem*. **271**: 31372-31378.

Kundakovic, M. and Champagne, F. A. (2011). Epigenetic perspective on the developmental effects of bisphenol A. *Brain Behav Immun*.

Kwon, S., Stedman, D. B., Elswick, B. A., Cattley, R. C. and Welsch, F. (2000). Pubertal development and reproductive functions of Crl:CD BR Sprague-Dawley rats exposed to bisphenol A during prenatal and postnatal development. *Toxicol Sci*. **55**: 399-406.

Lee, M. J., Lin, H., Liu, C. W., Wu, M. H., Liao, W. J., Chang, H. H., Ku, H. C., Chien, Y. S., Ding, W. H. and Kao, Y. H. (2008). Octylphenol stimulates resistin gene expression in 3T3-L1 adipocytes via the estrogen receptor and extracellular signal-regulated kinase pathways. *Am J Physiol Cell Physiol*. **294**: C1542-1551.

Makaji, E., Raha, S., Wade, M. G. and Holloway, A. C. (2011). Effect of Environmental Contaminants on Beta Cell Function. *Int J Toxicol*.

Masuno, H., Iwanami, J., Kidani, T., Sakayama, K. and Honda, K. (2005). Bisphenol a accelerates terminal differentiation of 3T3-L1 cells into adipocytes through the phosphatidylinositol 3-kinase pathway. *Toxicol Sci*. **84**: 319-327.

Masuno, H., Kidani, T., Sekiya, K., Sakayama, K., Shiosaka, T., Yamamoto, H. and Honda, K. (2002). Bisphenol A in combination with insulin can accelerate the conversion of 3T3-L1 fibroblasts to adipocytes. *J Lipid Res*. **43**: 676-684.

Matsushima, A., Teramoto, T., Okada, H., Liu, X., Tokunaga, T., Kakuta, Y. and Shimohigashi, Y. (2008). ERRgamma tethers strongly bisphenol A and 4-alpha-cumylphenol in an induced-fit manner. *Biochem Biophys Res Commun*. **373**: 408-413.

Melzer, D., Rice, N. E., Lewis, C., Henley, W. E. and Galloway, T. S. (2010). Association of urinary bisphenol a concentration with heart disease: evidence from NHANES 2003/06. *PLoS One*. **5**: e8673.

Miyawaki, J., Sakayama, K., Kato, H., Yamamoto, H. and Masuno, H. (2007). Perinatal and postnatal exposure to bisphenol a increases adipose tissue mass and serum cholesterol level in mice. *J Atheroscler Thromb*. **14**: 245-252.

Moriyama, K., Tagami, T., Akamizu, T., Usui, T., Saijo, M., Kanamoto, N., Hataya, Y., Shimatsu, A., Kuzuya, H. and Nakao, K. (2002). Thyroid hormone action is disrupted by bisphenol A as an antagonist. *J Clin Endocrinol Metab*. **87**: 5185-5190.

Nadal, A., Ropero, A. B., Laribi, O., Maillet, M., Fuentes, E. and Soria, B. (2000). Nongenomic actions of estrogens and xenoestrogens by binding at a plasma membrane receptor unrelated to estrogen receptor alpha and estrogen receptor beta. *Proc Natl Acad Sci U S A*. **97**: 11603-11608.

Nakagawa, Y. and Tayama, S. (2000). Metabolism and cytotoxicity of bisphenol A and other bisphenols in isolated rat hepatocytes. *Arch Toxicol*. **74**: 99-105.

Newbold, R. R., Padilla-Banks, E., Snyder, R. J. and Jefferson, W. N. (2005). Developmental exposure to estrogenic compounds and obesity. *Birth Defects Res A Clin Mol Teratol*. **73**: 478-480.

Nikaido, Y., Yoshizawa, K., Danbara, N., Tsujita-Kyutoku, M., Yuri, T., Uehara, N. and Tsubura, A. (2004). Effects of maternal xenoestrogen exposure on development of the reproductive tract and mammary gland in female CD-1 mouse offspring. *Reprod Toxicol*. **18**: 803-811.

Nishizawa, H., Morita, M., Sugimoto, M., Imanishi, S. and Manabe, N. (2005). Effects of in utero exposure to bisphenol A on mRNA expression of arylhydrocarbon and retinoid receptors in murine embryos. *J Reprod Dev*. **51**: 315-324.

Okada, H., Tokunaga, T., Liu, X., Takayanagi, S., Matsushima, A. and Shimohigashi, Y. (2008). Direct evidence revealing structural elements essential for the high binding ability of bisphenol A to human estrogen-related receptor-gamma. *Environ Health Perspect*. **116**: 32-38.

Palanza, P. L., Howdeshell, K. L., Parmigiani, S. and vom Saal, F. S. (2002). Exposure to a low dose of bisphenol A during fetal life or in adulthood alters maternal behavior in mice. *Environ Health Perspect*. **110 Suppl 3**: 415-422.

Phrakonkham, P., Viengchareun, S., Belloir, C., Lombes, M., Artur, Y. and Canivenc-Lavier, M. C. (2008). Dietary xenoestrogens differentially impair 3T3-L1 preadipocyte differentiation and persistently affect leptin synthesis. *J Steroid Biochem Mol Biol*. **110**: 95-103.

Pottenger, L. H., Domoradzki, J. Y., Markham, D. A., Hansen, S. C., Cagen, S. Z. and Waechter, J. M., Jr. (2000). The relative bioavailability and metabolism of bisphenol A in rats is dependent upon the route of administration. *Toxicol Sci*. **54**: 3-18.

Quesada, I., Fuentes, E., Viso-Leon, M. C., Soria, B., Ripoll, C. and Nadal, A. (2002). Low doses of the endocrine disruptor bisphenol-A and the native hormone 17beta-estradiol rapidly activate transcription factor CREB. *FASEB J*. **16**: 1671-1673.

Rangwala, S. M. and Lazar, M. A. (2000). Transcriptional control of adipogenesis. *Annu Rev Nutr*. **20**: 535-559.

Richter, C. A., Birnbaum, L. S., Farabollini, F., Newbold, R. R., Rubin, B. S., Talsness, C. E., Vandenbergh, J. G., Walser-Kuntz, D. R. and vom Saal, F. S. (2007). In vivo effects of bisphenol A in laboratory rodent studies. *Reprod Toxicol*. **24**: 199-224.

Ropero, A. B., Alonso-Magdalena, P., Garcia-Garcia, E., Ripoll, C., Fuentes, E. and Nadal, A. (2008). Bisphenol-A disruption of the endocrine pancreas and blood glucose homeostasis. *Int J Androl*. **31**: 194-200.

Ropero, A. B., Soria, B. and Nadal, A. (2002). A nonclassical estrogen membrane receptor triggers rapid differential actions in the endocrine pancreas. *Mol Endocrinol*. **16**: 497-505.

Rubin, B. S., Murray, M. K., Damassa, D. A., King, J. C. and Soto, A. M. (2001). Perinatal exposure to low doses of bisphenol A affects body weight, patterns of estrous cyclicity, and plasma LH levels. *Environ Health Perspect*. **109**: 675-680.

Ryan, K. K., Haller, A. M., Sorrell, J. E., Woods, S. C., Jandacek, R. J. and Seeley, R. J. (2010). Perinatal exposure to bisphenol-a and the development of metabolic syndrome in CD-1 mice. *Endocrinology*. **151**: 2603-2612.

Sajiki, J., Yanagibori, R. and Kobayashi, Y. (2010). Study of experiment on leaching of bisphenol A from infant books to artificial saliva. *Nihon Eiseigaku Zasshi*. **65**: 467-470.

Sakurai, K., Kawazuma, M., Adachi, T., Harigaya, T., Saito, Y., Hashimoto, N. and Mori, C. (2004). Bisphenol A affects glucose transport in mouse 3T3-F442A adipocytes. *Br J Pharmacol*. **141**: 209-214.

Sargis, R. M., Johnson, D. N., Choudhury, R. A. and Brady, M. J. (2010). Environmental endocrine disruptors promote adipogenesis in the 3T3-L1 cell line through glucocorticoid receptor activation. *Obesity (Silver Spring)*. **18**: 1283-1288.

Scherer, P. E., Williams, S., Fogliano, M., Baldini, G. and Lodish, H. F. (1995). A novel serum protein similar to C1q, produced exclusively in adipocytes. *J Biol Chem*. **270**: 26746-26749.

Schonfelder, G., Wittfoht, W., Hopp, H., Talsness, C. E., Paul, M. and Chahoud, I. (2002). Parent bisphenol A accumulation in the human maternal-fetal-placental unit. *Environ Health Perspect*. **110**: A703-707.

Seidlova-Wuttke, D., Jarry, H., Christoffel, J., Rimoldi, G. and Wuttke, W. (2005). Effects of bisphenol-A (BPA), dibutylphtalate (DBP), benzophenone-2 (BP2), procymidone (Proc), and linurone (Lin) on fat tissue, a variety of hormones and metabolic parameters: a 3 months comparison with effects of estradiol in ovariectomized rats. *Toxicology*. **213**: 13-24.

Simerly, R. B. (2008). Hypothalamic substrates of metabolic imprinting. *Physiol Behav*. **94**: 79-89.

Somm, E., Schwitzgebel, V. M., Toulotte, A., Cederroth, C. R., Combescure, C., Nef, S., Aubert, M. L. and Huppi, P. S. (2009). Perinatal exposure to bisphenol a alters early adipogenesis in the rat. *Environ Health Perspect*. **117**: 1549-1555.

Steppan, C. M. and Lazar, M. A. (2004). The current biology of resistin. *J Intern Med*. **255**: 439-447.

Tabb, M. M. and Blumberg, B. (2006). New modes of action for endocrine-disrupting chemicals. *Mol Endocrinol*. **20**: 475-482.

Takeuchi, T. and Tsutsumi, O. (2002). Serum bisphenol a concentrations showed gender differences, possibly linked to androgen levels. *Biochem Biophys Res Commun*. **291**: 76-78.

Taylor, J. A., Vom Saal, F. S., Welshons, W. V., Drury, B., Rottinghaus, G., Hunt, P. A., Toutain, P. L., Laffont, C. M. and VandeVoort, C. A. (2011). Similarity of bisphenol A pharmacokinetics in rhesus monkeys and mice: relevance for human exposure. *Environ Health Perspect*. **119**: 422-430.

Trasande, L., Ziebold, C., Schiff, J. S., Wallinga, D., McGovern, P. and Oberg, C. N. (2008). The role of the environment in pediatric practice in Minnesota: attitudes, beliefs, and practices. *Minn Med*. **91**: 36-39.

Vandenberg, L. N., Maffini, M. V., Sonnenschein, C., Rubin, B. S. and Soto, A. M. (2009). Bisphenol-A and the great divide: a review of controversies in the field of endocrine disruption. *Endocr Rev*. **30**: 75-95.

Vandenberg, L. N., Maffini, M. V., Wadia, P. R., Sonnenschein, C., Rubin, B. S. and Soto, A. M. (2007). Exposure to environmentally relevant doses of the xenoestrogen bisphenol-A alters development of the fetal mouse mammary gland. *Endocrinology*. **148**: 116-127.

Volkel, W., Colnot, T., Csanady, G. A., Filser, J. G. and Dekant, W. (2002). Metabolism and kinetics of bisphenol a in humans at low doses following oral administration. *Chem Res Toxicol*. **15**: 1281-1287.

vom Saal, F. S., Cooke, P. S., Buchanan, D. L., Palanza, P., Thayer, K. A., Nagel, S. C., Parmigiani, S. and Welshons, W. V. (1998). A physiologically based approach to the study of

bisphenol A and other estrogenic chemicals on the size of reproductive organs, daily sperm production, and behavior. *Toxicol Ind Health.* **14**: 239-260.

vom Saal, F. S., Timms, B. G., Montano, M. M., Palanza, P., Thayer, K. A., Nagel, S. C., Dhar, M. D., Ganjam, V. K., Parmigiani, S. and Welshons, W. V. (1997). Prostate enlargement in mice due to fetal exposure to low doses of estradiol or diethylstilbestrol and opposite effects at high doses. *Proc Natl Acad Sci U S A.* **94**: 2056-2061.

Wada, K., Sakamoto, H., Nishikawa, K., Sakuma, S., Nakajima, A., Fujimoto, Y. and Kamisaki, Y. (2007). Life style-related diseases of the digestive system: endocrine disruptors stimulate lipid accumulation in target cells related to metabolic syndrome. *J Pharmacol Sci*. **105**: 133-137.

Wei, J., Lin, Y., Li, Y., Ying, C., Chen, J., Song, L., Zhou, Z., Lv, Z., Xia, W., Chen, X. and Xu, S. (2011). Perinatal exposure to bisphenol A at reference dose predisposes offspring to metabolic syndrome in adult rats on a high-fat diet. *Endocrinology*. **152**: 3049-3061.

Woods, S. C. and D'Alessio, D. A. (2008). Central control of body weight and appetite. *J Clin Endocrinol Metab*. **93**: S37-50.

Xia, X. and Serrero, G. (1999). Inhibition of adipose differentiation by phosphatidylinositol 3-kinase inhibitors. *J Cell Physiol*. **178**: 9-16.

Xiao, X. Q., Williams, S. M., Grayson, B. E., Glavas, M. M., Cowley, M. A., Smith, M. S. and Grove, K. L. (2007). Excess weight gain during the early postnatal period is associated with permanent reprogramming of brown adipose tissue adaptive thermogenesis. *Endocrinology*. **148**: 4150-4159.

Yang, Y. J., Hong, Y. C., Oh, S. Y., Park, M. S., Kim, H., Leem, J. H. and Ha, E. H. (2009). Bisphenol A exposure is associated with oxidative stress and inflammation in postmenopausal women. *Environ Res*. **109**: 797-801.

Zalko, D., Jacques, C., Duplan, H., Bruel, S. and Perdu, E. (2011). Viable skin efficiently absorbs and metabolizes bisphenol A. *Chemosphere*. **82**: 424-430.



 