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1 **Is Bisphenol A an environmental obesogen?**

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25 **Key words:** Bisphenol a, obesity, endocrine disruptor, environmental obesogenic compounds

26

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28

29 **ABSTRACT**

30

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

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50

51 **INTRODUCTION**

52

53 Although 600 million people are currently facing energy deficits exposing them to
54 undernutrition, 1.9 billion people worldwide are overweight, with 600 million of those
55 classified as obese [1]. The growing rate of overweight and obese individuals clearly
56 characterizes the current worldwide “nutrition paradox”. Whereas undernutrition has declined
57 since 2007, obesity is now considered an epidemic and affects both adults and children [1]. An
58 increase in caloric intake and a decrease of energy expenditure are the main risk factors for
59 developing obesity. However, this energy imbalance, as well as genetic predispositions, do not
60 seem to be fully responsible for the epidemiological rise of obesity worldwide [2]. Growing
61 evidence strongly suggests that environmental chemicals, and particularly endocrine disruptors
62 (EDs), are an additional risk factor explaining the global obesity epidemic [3–5]. The term
63 “endocrine disruptor” was first mentioned in the 1990s and is historically associated with the
64 field of developmental organs, reproductive toxicology and wildlife biology [6]. An ED is
65 precisely defined as a substance or an exogenous mixture that is able to interfere with the
66 endocrine system and consequently cause adverse effects in a healthy organism, its progeny, or
67 other subpopulations [7]. Through the secretion of adipokines, adipose tissue is considered an
68 endocrine organ and can be targeted by EDs, thus potentially leading to adipose tissue
69 dysfunction and inflammation. These biological disorders appear during the pathophysiology
70 of obesity and confirm the causative link between ED exposure and the “obesogen hypothesis”
71 [3,8–10]. Obesogens are defined as chemicals that inappropriately alter metabolic functions
72 such as lipid homeostasis and fat storage, energy balance, regulation of appetite and satiety in
73 order to increase fat accumulation and, eventually, lead to the development of obesity [11–13].
74 Bisphenol a (BPA) was one of the first compounds identified as an obesogen alongside
75 pesticides, heavy metals, polychlorinated bisphenyls (PCBs) [3,5,14]. BPA is a plastic and
76 thermal paper component ubiquitously present in the environment and possesses estrogenic
77 activity. Numerous controversial discussions concerning the impact of BPA exposure on human
78 health are still debated despite emerging data demonstrating that BPA is associated with
79 infertility, cancer and metabolic disorders like obesity [8,9].

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

82

83

84 **OBESOGENIC ACTIVITY OF BISPHENOL A**

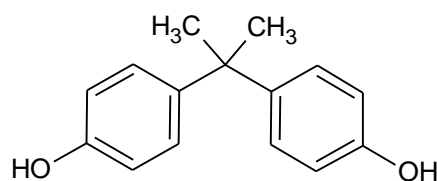
85

86 1 – BPA

87

88 BPA (4,4'-isopropylidenediphenol or 2,2'-bis(4-hydroxyphenyl)-propane, CAS 80-
89 05-7) is a white crystalline compound with a molecular weight of 228.29 g/mol, a melting-point
90 of 156 °C and a water-octanol partition coefficient (logP) of 3.32, and is relatively soluble in
91 lipophilic phases with low solubility in water (Figure 1) [15].

92



93

94

Figure 1: Molecular structure of BPA

95

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

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

108 In the USA, the Food and Drug Administration (FDA) banned the presence of BPA
109 in products designed for infants and toddlers in 2012 and in 2014 published a draft assessment
110 of the available literature and data on BPA. This draft assessment indicated that the “no
111 observed adverse effect level” (NOAEL) was 5 mg/kg of body weight per day without any
112 definition of a total daily intake (TDI). In contrast, Japan adopted a similar TDI as the EFSA
113 [21]. After a study reviewing the health risk assessment of BPA from food packaging
114 applications in 2013, the Minister of Health of Canada recommended that the general principle

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

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

123

124 2 - BPA exposure

125

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

134 BPA can also be released from epoxy resin lining of pipes leading to an increase of
135 BPA levels in drinking water [25]. Consequently, BPA has been found in drinking water at
136 concentrations ranging from 0.014 to 0.317 $\mu\text{g/L}$ and in water bottles at concentrations from
137 0.07 to 4.21 $\mu\text{g/L}$ [26,27]. Furthermore, human exposure to BPA can occur from non-dietary
138 sources such as air (indoor and outdoor), cosmetics, thermal paper, dust, toys, cars and more
139 [15,28].

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

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

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

155 BPA is now well characterized as an ED but its glucuronide conjugate does not show
156 estrogenic activity [45,46]. However, BPA-G has been shown to induce adipogenesis through
157 an ER-independent pathway, confirming the complexity of the effects of BPA exposure [47].
158

159 3 - Impact of BPA in obesity

160 *Epidemiological studies*

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

163 Rochester JR et al. (2013) reviewed the literature up to 2013 of BPA and its effects on
164 human health and described that obesity and body weight were two of the most studied
165 endpoints [8]. Nine of the ninety one articles analyzed reported that higher urinary or blood
166 BPA concentration was significantly correlated with higher BMI or body weight [8]. However,
167 because of the cross-sectional nature of these studies and controversial data, Rochester JR
168 concluded that causal links may be complex and consequently difficult to interpret [8]. Lakind
169 JS *et al.* (2014) reviewed the literature concerning the association of BPA exposure and diseases
170 like obesity, diabetes and cardiovascular events. In this review, nine articles were selected that
171 did not give evidence of a positive association between BPA exposure and obesity, BMI, waist
172 circumference and body weight. Moreover, this review included studies carried out at single
173 time point in adults, children and pregnant women and made interpretations for this population.
174 This review also highlighted some controversial data [48]. Mirmira P and Evans-Molina C
175 (2014) summarized human epidemiologic studies that have investigated links between BPA
176 levels and obesity. Ten articles were selected that primarily showed associations between
177 urinary BPA levels and obesity. However, no information about the criteria of selection of the
178 articles was given and this work also highlights a number of caveats and controversies that
179 should be considered in the article's interpretation [49]. Oppeneer S and Robien K (2015)
180 supplied a detailed analysis and review of literature concerning the obesogenic activity of BPA

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

191 However, as described above, obesity is a pathological condition with excessive fat
192 mass. Adipose tissue is now considered an endocrine organ that actively secretes a number of
193 adipokines. Zhao H.Y. *et al.* (2012) highlighted that high BPA exposure was associated with
194 higher urinary levels of leptin, an adipokine that acts to induce satiety and regulates long term
195 energy balance [52]. Elevated leptin levels contribute over time to the development of leptin
196 resistance, a contributing factor to increase in fat mass [53,54]. More recently, Rönn M. *et al.*
197 (2014) showed that increased adiponectin, an adipokine secreted in order to counteract insulin
198 resistance, and leptin circulating levels were associated with an increased BPA level even
199 without an increase in fat mass. In this study, which was performed with 870 subjects >70 years
200 of age, elevated BPA levels were also associated with a decrease in ghrelin level [55]. Ghrelin
201 is a hormone released from organs of the digestive system and from the hypothalamus and
202 possesses orexigenic activity. Ghrelin is also known as a short and long term regulator of body
203 weight and low ghrelin levels are associated with obesity in human patients [56,57]. Thus, these
204 studies suggest that elevated BPA exposure is associated with changes in adipokine levels that
205 are involved in regulation of appetite and satiety and generally associated with the
206 pathophysiology of obesity. From these data it seems that adipose tissue is a target of BPA and
207 produces adipocyte dysfunction.

208 *Limitations for epidemiological studies*

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

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

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

225

226 *Infant / in utero exposure*

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

231 Table I: Summary of epidemiological studies regarding prenatal and early-life exposure to
 232 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 st and 3 rd 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 rd 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 nd and 3 rd 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 rd 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 st 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 rd 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]

233 %BF: % of Body Fat, BMI: Body Mass Index, BW: Body Weight, FMI: Fat Mass Index, HC: Having Weight,
234 ST: Skinfold Thickness, WC: Waist Circumference

235 Collectively, most data from epidemiological studies performed in adulthood (11/16)
236 indicates that BPA exposure during developmental periods is associated with an increased risk
237 of programmed obesity. However, the presence of studies showing no association or an opposite
238 correlation does not allow this to be a definitive conclusion. In agreement with Braun JM
239 (2016), we observed that available epidemiological data concerning the obesogenic activity of
240 BPA is ambiguous [51]. Indeed, there are multiple sources of BPA exposure and obesity is a
241 complex pathology for which the definition is still debated [74–76]. Moreover, evaluation of
242 obesity in infants and children appears to be imprecise, notably by the disregard of additional
243 parameters such as height. Thus, epidemiological studies should be more focused on other
244 metabolic disorders such as glucose tolerance, insulin resistance, triglycerides and cholesterol
245 levels, adipokines secretion and inflammatory markers such as circulating cytokines [39,77,78].

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

249 *In vivo studies*

250 Numerous studies have been published concerning the pathophysiology of obesity after
251 BPA exposure in animals. In most of these reports, mice or rats were used and treated daily
252 with 5 to 5000 $\mu\text{g}/\text{kg}$ BPA by gavage or in drinking water for 4 weeks to 8 months. Conversely
253 to the epidemiological trend, no increase in body weight was observed at the end of these
254 experiments with BPA supplementation [79–82]. Nevertheless, animals treated with low doses
255 of BPA presented metabolic dysfunctions associated with obesity including increased
256 expression of genes involved in fatty acid metabolism, cholesterol and triglyceride biosynthesis
257 [79]. These metabolic disorders are also found in animals fed with high fat diet (HFD) compared
258 to animals fed with standard diet [82].

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

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

273

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) ^o [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 (C57B16)	100 µg/kg/d, SC	Standard	GD6-PND0-PND21	↓ PNM3-8 ↑ PNM3-8 = PNM3-8		↓ glucose tolerance ↓ glucose tolerance ↓ glucose tolerance	Liu J. <i>et al.</i> (2013) [106]
Mice (C57B16/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 M F		Others effects regarding the pathophysiology of obesity	Ref.
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.							

274 Table II depicts that a majority of studies, although notably not all (13/24 for males and
275 8/15 for females), reported an association between prenatal exposure of BPA and an increased
276 body weight of animal pups. Some studies also reported no association (8/24 for males and 3/15
277 for females) and others reported an inverse correlation (2/24 for males and 4/15 for females).
278 These divergent results, as in the epidemiological studies, raise concerns about the data and do
279 not allow definitive conclusions. The central difficulty is the variability of methods that differ
280 in terms of doses, window of exposure and age of animal pups at the end of the experiments.
281 Despite a large library of available literature, one cannot identify a precise window and dose of
282 exposure to BPA that is responsible for an increased risk to develop obesity. Liu J. *et al.* (2013)
283 well demonstrated the differences in body weight variations of mice between different windows
284 of exposure (prenatal, lactation or both) for the same dose of BPA [106].

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

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

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

310 *In vitro studies*

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

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

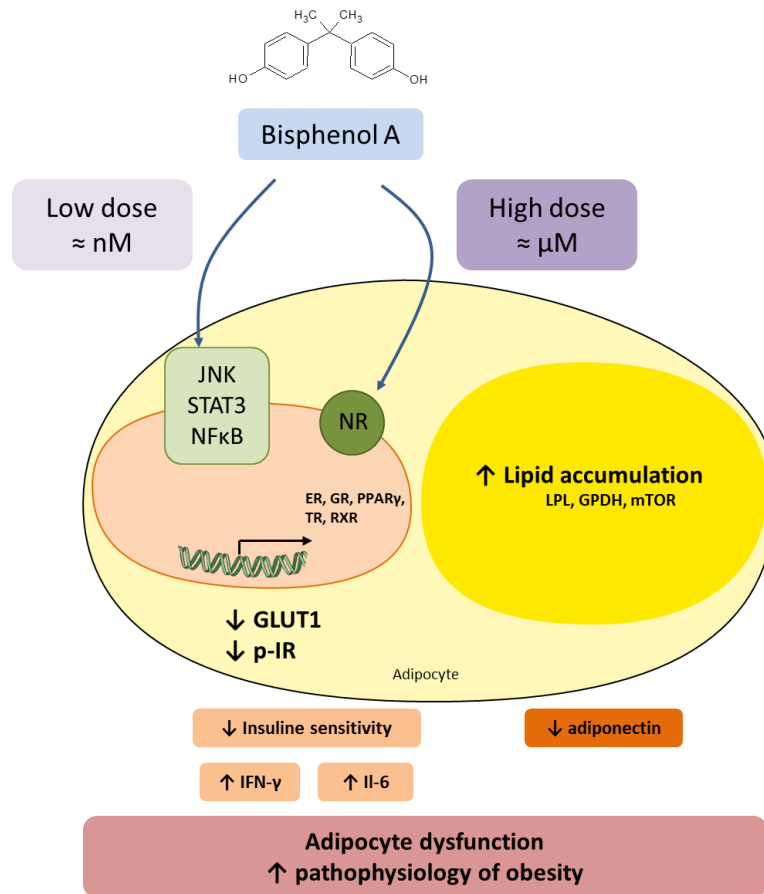
335 Several molecular targets have been identified to explain the obesogenic effect of BPA
336 [39,51,125]. Indeed, it has been reported that BPA, in concentration ranges of μ M, interacts
337 with Nuclear Receptors (NR), Estrogen Receptors (ER), Glucocorticoid Receptors (GR),

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

342 Furthermore, activation of C/EBP- α , LPL and mammalian Target Of Rapamycin
343 (mTOR), which are involved in lipogenesis and adipokine secretion, has also been described
344 after adipocyte exposure to BPA, concurrent with a decrease of adiponectin secretion
345 [121,126,128,135]. Thus, BPA induces inflammatory activation, adipogenesis and lipogenesis
346 pathways and modulates adipokine secretion contributing to adipocyte dysfunction, which may
347 explain lipid accumulation and the increase of fat mass observed (Figure 2). These results are
348 in agreement with those from human and animal studies and confirm the impact of BPA
349 exposure on adipocyte dysfunction found in obesity.

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

357



358

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

361

362 *Epigenetics:*

363 Several data have demonstrated the ability of BPA to induce genetic modifications with
364 dramatic consequences on reproductive functions and cancer development [136,137]. However,
365 available data regarding the impact of BPA exposure on genetic aspects of obesity remains
366 sparse so far. Among genome-wide association studies (GWAS) findings, the locus *fat mass*
367 *and obesity associated (FTO)* was described as the most associated gene with an increased
368 BMI, each risk allele of this locus increasing risk of obesity from 20 % to 30 % in humans
369 [138–141]. Other genes regulating expression of signaling molecules involved in glucose and
370 lipid homeostasis and in feeding behavior were also identified such as those encoding
371 *melanocortin receptors (MCRs)*, *proopiomelanocortin (POMC)*, *Agouti* or *brain-derived*
372 *neurotrophic factor (BDNF)* [140]. The regulation of gene expression is predominantly
373 mediated by DNA methylation, RNA silencing, histone acetylation and nucleosome
374 remodeling, four epigenetic mechanistic processes [142–144]. In the viable yellow Agouti (A

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

382

383

384 **CONCLUSION and PERSPECTIVES**

385

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

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

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

416

417

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