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1 **Endocrine disrupting chemicals and metabolic disorders in the liver: what if we also looked**
2 **at the female side?**

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19

20 **Abstract :**

21 Endocrine disrupting chemicals (EDCs) are linked to the worldwide epidemic incidence of metabolic disorders
22 and fatty liver diseases, which affects quality of life and represents a high economic cost to society. Energy
23 homeostasis exhibits strong sexual dimorphic traits, and metabolic organs respond to EDCs depending on sex,
24 such as the liver, which orchestrates both drug elimination and glucose and lipid metabolism. In addition, fatty
25 liver diseases show a strong sexual bias, which in part could also originate from sex differences observed in gut
26 microbiota. The aim of this review is to highlight significant differences in endocrine and metabolic aspects of
27 the liver, between males and females throughout development and into adulthood. It is also to illustrate how
28 the male and female liver differently cope with exposure to various EDCs such as bisphenols, phthalates and
29 persistent organic chemicals in order to draw attention to the need to include both sexes in experimental studies.
30 Interesting data come from analyses of the composition and diversity of the gut microbiota in males exposed to
31 the mentioned EDCs showing significant correlations with hepatic lipid accumulation and metabolic disorders
32 but information on females is lacking or incomplete. As industrialization increases, the list of anthropogenic
33 chemicals to which humans will be exposed will also likely increase. In addition to strengthening existing
34 regulations, encouraging populations to protect themselves and promoting the substitution of harmful chemicals
35 with safe products, innovative strategies based on sex differences in the gut microbiota and in the gut-liver axis
36 could be optimistic outlook.

37

38 **Keywords :**

39 Endocrine disrupting chemicals ; liver ; sex-dimorphism ; estrogen ; growth hormone; gut microbiota

40 **1. Introduction**

41 Historically, the concept of endocrine disrupting chemicals (EDCs) emerged during the Wingspread
42 conference in 1991 to explain the many observations made in wildlife, for example on the decrease in bird
43 populations, particularly the bald eagles in California and the alligator populations in certain lakes from Florida.
44 These observations coincided with the widespread use of the insecticide dichlorodiphenyltrichloroethane (DDT)
45 in agriculture in the United States, which was banned in 1972. Experimental studies later demonstrated that DDT
46 could interfere with the thickening of bald eagle eggshell (Grier, 1982) and the sexual differentiation of male
47 alligators (Hamlin and Guillette, 2010) which are sex steroid dependent processes. The tragic event of
48 diethylstilbestrol (DES) also illustrated that human health was vulnerable to endocrine disruption. Between the
49 1940s and 1980s, millions of women received the estrogen synthetic to prevent miscarriages, which has led to
50 an increased prevalence of very rare vaginal and cervical clear cell carcinomas in girls. DES sons also suffered
51 from reproductive disorders and cancers (Fenichel et al., 2015, Colborn et al., 1993, Newbold et al., 1983). These
52 events suggested a causal relationship between exposure to chemicals and the later development of
53 reproductive disorders and cancer.

54 In 2002, the world health organization (WHO, 2002) defined the endocrine disruptor as “an exogenous
55 substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health
56 effects in an intact organism, or its progeny, or (sub)populations". Thus, endocrine disruption is characterized by
57 a modification of the endocrine system resulting in a deleterious adverse effect. For example, EDCs can mimic or
58 antagonize hormonal action and they can interfere with hormone production, transport or metabolism
59 (Diamanti-Kandarakis et al., 2009, Zoeller et al., 2012). While the main concern of EDCs was centered on the field
60 of reproductive research, a major step was taken with the demonstration that the male and female mice deficient
61 for the estrogen receptor ER (α) were not only sterile but obese and resistant to insulin. They also had bone and
62 cardiovascular defect. It illustrated that both sexes and more organs than previously thought could be under
63 estrogen regulation (Couse and Korach, 1999, Heine et al., 2000). In addition, EDCs were demonstrated to
64 interfere with several hormones not limited to the sex steroid hormones and to interact with various nuclear
65 receptors such as the peroxisome proliferator-activated receptor PPAR γ essential for fat differentiation (Rosen
66 et al., 1999), expanding the concept from endocrine disruption to disruption of energy homeostasis (Thayer et
67 al., 2012, Vandenberg et al., 2013, Casals-Casas and Desvergne, 2011, Nadal et al., 2017, Gore et al., 2015).

68 Energy homeostasis is a physiological function with strong sex-dimorphic traits (Mauvais-Jarvis, 2011). For
69 example, women are more susceptible to develop adrenal diseases causing metabolic disturbances, e.g., Cushing
70 syndrome (Audenet et al., 2013) while men will more often develop non-alcoholic fatty liver diseases (NAFLD)
71 and hepatocarcinoma (Ruggieri et al., 2010). In addition, males develop visceral obesity, which is very deleterious
72 as it triggers inflammation and insulin resistance as well as ectopic localization of fat resulting in lipotoxicity (e.g.,
73 NAFLD). On the contrary, circulating estrogens protect females from metabolic disorders (Barros et al., 2006,
74 Riant et al., 2009, Mauvais-Jarvis, 2015). However, while women make up half of the population, information is
75 lacking on the endocrine function of metabolic organs and the sex-specificities of detoxification. Until recently,
76 scientists had preferred to study male rodents rather than females because of their cyclical hormonal
77 fluctuations. Consequently, there is still a lack of data on the safe use of drugs in women (Lee and Wen, 2020),
78 which remained mainly determined on a body weight basis while women are the biggest users of drugs
79 (Manteuffel et al., 2014). This highlights the need for a more precise understanding of the consequences of
80 exposure to endocrine disruptors on energy homeostasis in females, especially in the liver. Indeed, the liver is a
81 highly sex dimorphic organ and in addition to being a major orchestrator of glucose and lipid metabolism, it is
82 the main site of detoxification (Mauvais-Jarvis, 2015, Waxman and Holloway, 2009, Fu et al., 2016).

83 This review provides an overview of the main liver sex dimorphic traits in relation to energy homeostasis and
84 drug elimination, with an emphasis on the underlying molecular determinants which may account for gender
85 susceptibility of fatty liver diseases. Another point of the review focuses on the main characteristics of EDCs that
86 may alter signaling pathways initiated by sex steroids, growth hormone (GH) and glucocorticoids. The review also

87 introduces the microbiota because it is likely to contribute to the maintenance of hepatic sexual dimorphism,
88 and it is a potential target of EDCs. Overall, the aim is to draw attention to the need to study both sexes because
89 it should help design sex-specific therapeutic drugs to prevent and / or counteract the deleterious effects of
90 exposure to pollutants and improve health of both women and men, throughout life.

91 **2. Sex-dimorphic traits of the liver**

92 The liver is highly dependent on sex from early life to puberty. Sex hormones have a decisive role in this step-
93 tiered process initially orchestrated by the perinatal surge of testosterone in males which exerts an
94 “organizational” role while after the onset of puberty estrogens and androgens will exert “activational” effects,
95 as reviewed elsewhere (Mauvais-Jarvis, 2015). In addition to sex steroid hormones, the secretory dynamics of
96 GH is prominent in the sex-dimorphic gene expression in liver. The neonatal testosterone surge has programming
97 activities not only in the brain where it triggers eating behavior and energy expenditure (Nohara et al., 2013),
98 but also in the liver (Della Torre et al., 2018). Mechanisms of actions involve the aromatase-dependent
99 conversion of testosterone to estradiol in the hypothalamus, as evidenced using aromatase KO (ArKO) mice and
100 pharmacological interventions such as treatment of males with an aromatase inhibitor, neonatal androgenization
101 of females, or female treatment with estradiol benzoate (Della Torre et al., 2018, Mauvais-Jarvis, 2015, Nohara
102 et al., 2013). This dictates the pattern of expression of ER α in the liver (Zheng et al., 2018; Della Torre et al., 2018)
103 and the pulsatility of GH secretion which does not manifest until after weaning and controls growth, obesity and
104 sexual dimorphism of hepatic gene expression (Lichanska and Waters, 2008). With aging, the liver exhibits a
105 decrease in the marks of sex-dimorphism due to the decline in plasma levels of GH (and of pulsatility in males)
106 and of gonadal hormones (Lichanska and Waters, 2008, Mauvais-Jarvis, 2015). Obesity in men also causes a
107 striking negative effect on the pulsatility of GH secretion feminizing the liver (Roelfsema and Veldhuis, 2016).

108 **2.1. Sex differences in the expression of nuclear receptors involved in glucose and lipid metabolism, and** 109 **drug disposal**

110 There are fundamental sex differences in the use of lipids and carbohydrates between males and females. In
111 females, lipid synthesis and energy storage would be an evolutionary strategy to maintain reproductive capacity
112 in times of food scarcity, while the mobilization of carbohydrates as a fuel source would provide males with
113 immediate energy for muscle activity (Mauvais-Jarvis, 2015). Energy homeostasis in the liver is largely
114 orchestrated by specific nuclear receptors of the NR1 family, namely peroxysome proliferated activated
115 receptors (PPAR α , β/δ), liver X receptors (LXR α , β), farnesoid X receptor (FXR), constitutive androstane receptor
116 (CAR) and pregnane X receptor (PXR). Their heterodimerization with retinoid X receptor (RXR) activates
117 complexed downstream signaling events. These transcription factors act as sensors of the environmental or
118 hormone signals to maintain homeostasis between the fed and fasting states, to keep fat content of hepatocytes
119 at low levels in physiological conditions. Activated NRs differ according to sex giving rise to clusters of cross-
120 interacting NRs which received the name of “interactome” by Rando and Wahli (Rando and Wahli, 2011). While
121 PPARs, LXR and FXR were first identified as sensors of endobiotics (fatty acids, eicosanoids, oxysterols...), CAR,
122 PXR as well as the aryl hydrocarbon receptor (AHR), were first identified as sensors of xenobiotic and drugs,
123 promoting their clearance (Hakkola et al., 2018, Cave et al., 2016, Casals-Casas and Desvergne, 2011). AHR, CAR,
124 PXR and PPAR regulate in coordinated networks, the expression of phase I drug metabolizing enzymes such as
125 the cytochrome P450 monooxygenases of the CYP1A, CYP2B, CYP3A and CYP4A family members, which
126 metabolize steroids, fatty acids in addition to lipophilic drugs and xenobiotics, phase II enzymes and transporters
127 (Aleksunes and Klaassen, 2012, Danielson, 2002, Choudhary et al., 2004, Monostory et al., 2009). Several of these
128 receptors/transcription factors and target genes exhibit sex-biased expression levels in several species (rat,
129 mouse, chicken, and dog) as well as in humans although to a lower extent (Waxman and Holloway, 2009, Shapiro
130 et al., 1995). For example, *Cyp2b9*, *Cyp2b10*, *Cyp3a11*, *Cyp4a10* phase I enzymes and *Sult1e1*, a phase II
131 sulfotransferase involved in estrogen metabolism are more highly expressed in females than males. In contrast,
132 *Cyp2b19*, *Cyp2d9*, and *Cyp4a12* and phase II enzymes involved in testosterone biosynthesis and metabolism (e.g.,
133 *Hsd3b5*) are more expressed in males than females (Clodfelter et al., 2006). Sex differences are not limited to

134 drug metabolizing enzymes (DMEs). A comprehensive microarray analysis of mouse liver revealed that about
135 70% of genes were expressed in a sex-dimorphic way. In addition to differences in hepatic drug metabolism, the
136 main determinant of liver sex differences, sex differences were also found in relation with protease inhibitory
137 activities, carboxylic acid, fatty acid, steroid and lipid metabolic pathways but also immune/defense response
138 and CD antigens, and inflammatory pathways with differences in expression of chemokines and cytokines (Yang
139 et al., 2006). Deregulation of these pathways primarily regulated by sex steroids and the secretory dynamics of
140 GH may favor the development of sex-biased liver diseases (Fig. 1).

141

142

2.2. Regulation by sex steroids and hepatic ER α and AR

143 Comparative analysis of hepatic genes in male and female mice showed that the expression of major sexually
144 dimorphic genes was initiated at birth and was regulated by ER α (Zheng et al., 2018). Indeed, males show higher
145 levels of ER α in the liver than females in neonatal mice and males but not females with ER α -specific hepatic
146 disruption from the embryonic stage (liver-specific ER α knockout mice or LERKO) expressed lower amount of
147 androgen receptor (AR) in adulthood than wild type mice (Della Torre et al., 2018). ER α is the predominant
148 estrogen receptor in the liver (Eisenfeld and Aten, 1987). At adulthood, ER α expression is higher in the liver of
149 female than male mice (Della Torre et al., 2018, Naville et al., 2013), which strongly suggests that ER α exerts sex-
150 dependent functions in the liver throughout development. Interestingly, exogenous administration of steroids
151 (E2 + dihydrotestosterone, DHT) reversed the NAFLD phenotype observed in male rats fed a high-fat diet,
152 enhancing expression levels of ER α and AR in liver and decreasing fatty acid and cholesterol synthesis and
153 increasing β -oxidation; thus indicating that maintenance of lipid homeostasis in males depends on both estrogen
154 and androgen signaling (Zhang et al., 2013). In addition, male but not female mice lacking hepatic AR exhibit
155 steatosis and insulin resistance (Lin et al., 2008), and hepatic ER α is critical for regulation of gluconeogenesis and
156 lipid metabolism in adult males (Qiu et al., 2017). In females, hepatic ER α could couple lipid metabolism in the
157 liver to the reproductive cycle to adapt hepatic lipid metabolism to the needs of reproductive functions,
158 especially in the event of food shortage (Della Torre et al., 2016). In a situation of excess dietary lipids, the hepatic
159 ER α would counteract steatosis (Meda et al., 2020) through mechanisms which may involve the anorectic
160 hepatokine GDF15 (Guillaume et al., 2019). However, other authors reported minor changes in both LERKO males
161 and females, even when exposed to a high-fat diet (Matic et al., 2013). The other estrogen receptors, the G-
162 coupled protein 30 receptor (*Gper1*) and the ER β which are expressed (although weakly) in the liver of rodents
163 and humans (Martensson et al., 2009, Isensee et al., 2009, Prossnitz and Barton, 2014) have not yet been shown
164 to contribute to the liver sex-dimorphism.

165 Enzymes that regulate the local concentration of active estrogens also contribute to the sex-dimorphism of
166 the liver. Hepatic overexpression of the steroid sulfatase (STS), a desulfating enzyme that converts steroid
167 sulfates in hormonally active steroids, alleviated obesity and type 2 diabetes in mouse models of obesity in a sex-
168 dependent manner. In females, alleviation was driven by a liver-specific increase of estrogen activity leading to
169 enhanced hepatic insulin sensitivity and reduced steatosis and inflammation. These effects were estrogen
170 dependent since they were abolished by ovariectomy. In males, the metabolic benefit of hepatic overexpression
171 of STS resulted indirectly from a decrease of inflammation in both the white adipose tissue (WAT) and muscle.
172 This effect was not demonstrated in females (Jiang et al., 2014). Analysis of the metabolic consequences of the
173 global knockdown of the estrogen sulfotransferase (EST encoded by *Sult1e1*) also revealed sex-dimorphic effects
174 in mouse models of obesity and type 2 diabetes. EST sulfonates estrogens rendering them unable to bind ER α .
175 While a metabolic benefit was described in female mice due to increased estrogenic activity in the liver, an
176 aggravation of the metabolic disorders was observed in males (Gao et al., 2012). Interestingly, the primary events
177 observed in EST and STS mouse models differ between sex, occurring primary in liver for female mice and in the
178 WAT for male mice (Jiang et al., 2014, Gao et al., 2012).

179

2.3. Liver GHR and GH signaling events

180 GH regulates various aspects of liver physiology through activating the Janus kinase (JAK) 2- signal transducer
181 and activator of transcription (STAT) 5 pathway, and impairment of hepatic GH - JAK2 - STAT5 signaling is
182 associated with metabolic disturbances and obesity, aberrant glucose metabolism, and NAFLD development in
183 humans and mouse models (Cui et al., 2007). Mechanisms involve both enhanced PPAR γ and SREBP-1c signaling
184 leading to increased lipogenesis and enhanced expression of the transporter CD-36 triggering increased fatty
185 acid (FA) uptake. Accumulation of lipids promotes liver damage and cell death by increasing oxidative stress
186 (mitochondrial dysfunction) and liver inflammation (steatohepatitis), which over time can be accompanied by
187 varying degrees of liver fibrosis and liver cancer (Kaltenecker et al., 2019).

188 While pituitary GH secretion remains almost continuous in females, it becomes pulsatile in males starting from
189 puberty and this pattern of secretion dictates most of the GH signaling cascade including GH receptor (GHR),
190 JAK2 and STAT5 in mice, rats and humans (Kaltenecker et al., 2019). Thus, lack of circulating GH following
191 hypophysectomy led to the elimination of 90% of the sex differences in the liver, while exogenous administration
192 of GH in a pulsed (male) or continuous (female) manner restored the corresponding patterns of expression of
193 hepatic genes in males and females, respectively (Sasamura et al., 1990, Agrawal and Shapiro, 2001, Waxman
194 and O'Connor, 2006). Different transcription factors (TFs) involved in liver development contribute to the sexually
195 dimorphic expression in liver. Knockout strategies demonstrated that STAT5b was a major mediator of the sex-
196 dependent transcriptional response to GH in the liver. Its activation and phosphorylation state are directly
197 regulated by GH plasma level, either pulsatile in males, or low and persistent in females (Cui et al., 2007,
198 Clodfelter et al., 2006). Therefore, the loss of pulsatility of GH alters the kinetics of STAT5 signaling in males and
199 causes feminization of the liver, which can be reversed by administration of DHT (Oshida et al., 2016). If other
200 TFs which include HNF4 α exerting predominant effect in males co-regulating sexually dimorphic hepatic gene
201 expression with STAT5b (Holloway et al., 2006) and the female-biased activators FOXA1 (HNF3 α), FOXA2
202 (HNF3 β), ONECUT2 (HNF6 β) play a role in the liver metabolic regulation, STAT5b and the two STAT5b-dependent
203 repressors, the male-biased repressor BCL6 (i.e., it represses female-biased genes in male liver) and the female-
204 biased repressor CUX2 (i.e., it represses male-biased genes in female liver) are the key mediators (Sugathan and
205 Waxman, 2013, Lau-Corona et al., 2017, Oshida et al., 2016). Moreover, it was shown that this dynamic
206 transcription network also depends on the states of the hepatic chromatin and the accessibility to transcription
207 factors which are events regulated by GH according to sex (Lau-Corona et al., 2017). In females, E2 and GH
208 signaling regulate overlapping cellular networks related with physiological control of lipid and glucose
209 metabolism. For example, estrogens can modulate GH actions on liver by modulating GH responsiveness, which
210 include changes in hepatic GHR expression and crosstalk with GH-activated JAK2-STAT5 signaling pathway
211 (Fernandez-Perez et al., 2013).

212 Other molecular determinants such as glucocorticoid receptors (GR) which functions often as a cofactor of STAT5
213 for GH-induced genes regulate sex-biased inflammatory gene expression in the liver (Fig.1). Gene sets which
214 require physical STA5-GR interaction, include those controlling somatic growth, sexual maturation and
215 maintenance of energy homeostasis (Mueller et al., 2012). In addition in males, androgens have a positive control
216 over glucocorticoid signaling and stimulate the expression of 11 β -HSD which activate corticosteroids, while it is
217 antagonized by estrogens in females (Quinn and Cidlowski, 2016). Hence in aging females, when estradiol levels
218 drop, FSH levels increase and potentiate hepatic GR signaling leading to GC hypersensitivity and hepatic steatosis
219 resembling Cushing's syndrome (Quinn et al., 2018).

220

221 3. Fatty liver diseases and gender susceptibility

222 Worldwide obesity has nearly tripled since 1975. In 2016, more than 1.9 billion adults, 18 years and older, were
223 overweight; of these over 650 million were obese (WHO, 2018). Obesity predisposes to metabolic-related
224 diseases including non-alcoholic fatty liver disease (NAFLD) and other metabolic disorders grouped under the
225 term of metabolic syndrome, which significantly increases the cardiovascular risk of patients with glucose
226 metabolism alterations, and type 2 diabetes (Farrell and Larter, 2006, Anstee et al., 2013). NAFLD is one of the
227 most common causes of chronic liver injury worldwide. Its prevalence ranges from 24% in Europe and the United
228 States to 30 and 32 % in the South America and the Middle East, respectively (Younossi et al., 2018).

229 Approximately 10% of patients with NAFLD evolve to an irreversible—and chronic inflammatory state named
230 nonalcoholic steatohepatitis (NASH) of which 8% to 26% progress to cirrhosis, and 4% to 27% of those with
231 cirrhosis-NASH will develop hepatocellular carcinoma (HCC). These figures lead to theoretical HCC incidence rates
232 that ranges from 0.6 in 100,000 population to 210 in 100,000 population (Siegel and Zhu, 2009). HCC is the most
233 common primary liver cancer with a strong male bias. In 2012, one in four cases of liver cancer was attributable
234 to the combined effect of a high body mass index (BMI) and type 2 diabetes with a gender bias 3 times higher in
235 men than in women (Asrani et al., 2019). It indicates that gender is an important determinant of the development
236 of fibrosis in the progression of liver disease. Consistently, chemically induced mouse models of HCC show
237 enhanced secretion of inflammatory cytokine IL6 in males but not in females, which could be reduced by
238 administration of estradiol, highlighting the protective function of estrogens against the development of HCC
239 (Naugler et al., 2007). In addition, differential expression of wild-type and variant forms of estrogen receptors
240 was reported in normal liver and HCC. It may alter hormonal responsiveness and contribute to a disruption of
241 the balance between cell proliferation and cell death leading to hepatic carcinogenesis (Ruggieri et al., 2010). In
242 contrast to estrogens, androgens are profibrotic and carcinogenic, at least in the early stages of HCC development
243 (Grossmann et al., 2019). Nevertheless, the sex dependence of the molecular mechanisms of HCC formation and
244 progression in the context of NAFLD / NASH which may take decades to evolve remains elusive (Fig. 1), but insulin
245 resistance which triggers fat accumulation in hepatocytes and mitochondrial dysfunction and increased
246 production of reactive oxygen species have critical roles (Kaltenecker et al., 2019). Interestingly, female liver
247 mitochondria display a higher capacity and efficiency of substrate oxidation than male mitochondria (Justo et al.,
248 2005). Other signaling pathways deregulated in HCC involve growth factors, angiogenesis and cell cycle
249 regulators which contribute to chronic liver damage and progression up to dysplastic lesions and malignant
250 transformation, all of which may as well show gender disparity (Kaltenecker et al., 2019).
251 Contrariwise, auto-immune liver diseases (AILDs) (also rare diseases) are more frequent in women than in men
252 especially auto-immune hepatitis (AIH) and primary biliary cholangitis (PBC) while primary sclerosis cholangitis
253 (PSC) is equally distributed between sexes (Schwinge and Schramm, 2019). The female predominance in AIH and
254 PBC are among the strongest among AIDs, a range of diseases in which the immune response to self-antigens
255 results in damage or dysfunction of tissues. Mechanisms for female predominance are not elucidated but
256 underlying mechanisms include differences in the immune system, sex hormones including estrogens, androgens
257 but also progesterone and prolactin, genetics and X chromosomal inactivation as well as microbiome and the
258 environment (Schwinge and Schramm, 2019). Females are also more susceptible to acute liver failure and toxin-
259 mediated hepatotoxicity than males (Guy and Peters, 2013). Anatomical differences in the liver could also
260 account for gender susceptibility to liver diseases as females of the same body size and weight as males have a
261 smaller liver (Chan et al., 2006).

262
263

4. Gut microbiota and liver sex-dimorphism

264 The gut microbiota is subject to sex differences that have been proposed as the basis of sexual predisposition to
265 disease (Santos-Marcos et al., 2019). The liver is the first organ exposed to gut-derived factors, receiving all the
266 blood from the intestine through the portal vein, and it is acknowledged that dysbiosis, defined as changes in gut
267 microbiota composition and function associated with health defects, is associated with metabolic syndrome and
268 the development and progression of NAFLD through the gut-liver axis (Tripathi et al., 2018), regardless of body
269 mass index and insulin resistance (Da Silva et al., 2018). Associations are so strong that microbiota-derived
270 metabolites are considered as biomarkers of steatosis progression or even potential therapeutic targets of the
271 disease (Knudsen et al., 2019). For example, the production of the microbiota-derived metabolites short chain
272 fatty acids (SCFAs) such as propionate can cross the intestinal barrier and reach the liver through the portal vein
273 blood, reducing steatosis and inflammation by acting on the transcription of several rate-limiting step enzymes
274 involved in de novo lipogenesis (Tilg et al., 2016). It has also been proposed that SCFAs (e.g., butyrate) which can
275 potentiate GH secretion in the pituitary and its stimulating factor ghrelin could play a key role in sustaining
276 hepatic sexual dimorphism (Weger et al., 2019a). Ghrelin, produced by the enteroendocrine cells of the stomach
277 increases food intake. Stimulated by testosterone and inhibited by estradiol, ghrelin activates GH secretion

278 contributing to the amplitude of the secretion pattern (Weger et al., 2019a, Xie et al., 2015). The importance of
279 the microbiota in hepatic sexual dimorphism was also demonstrated in germ-free mice in which the male-type
280 pulsatile GH secretion is absent and which exhibit a feminized hepatic metabolism (Selwyn et al., 2015, Weger
281 et al., 2019a).

282

283 **5. EDCs and sex-specific metabolic disruption**

284 **5.1. Characteristics of various EDCs causing metabolic disruption**

285 More than 900 molecules present in the environment could be considered as endocrine disruptors according to
286 the World Health Organization (WHO / UNEP 2013). This number may change as other lists of potential endocrine
287 disruptors are proposed based on the review of the scientific literature (Karthikeyan et al., 2019). EDCs
288 encompass a variety of chemical classes such as pesticides and fungicides, products and by-products of the
289 chemical industry, compounds used in the plastics industry and in consumer products, pharmaceutical agents
290 and phytoestrogens. Humans are exposed to these chemicals in a variety of ways but food consumption is the
291 main route of exposure (Gore et al., 2015). Based on their degradability, chemicals may be either highly persistent
292 in the environment or non-persistent. Persistent Organic Pollutants (POPs) are highly lipophilic compounds with
293 low-degradability. POPs include organochlorine pesticides, such as DDT, industrial chemicals such as
294 polychlorinated biphenyls (PCBs, which were designed for their low flammability and high thermal conductivity
295 properties), or unintended by-products of many industrial processes, including dioxins which result from
296 incomplete combustions during industrial processes (but also during forest fires or volcanic eruptions). Since
297 2001, the Stockholm Convention regulates the production and use of POPs due to their serious adverse effects
298 on humans and the ecosystem (Ruzzin, 2012, Kassotis et al., 2020). For example, productions of DDT and PCBs
299 were banned and production of dioxins is strictly limited. However, the ability of POPs to bio-accumulate and
300 bio-magnify in ecosystems has caused the contamination of soil and sediments. POPs have also been found in
301 the adipose tissues of animals and humans where they can be stored for years (Milbrath et al., 2009) potentially
302 causing either obesogenic and/or proinflammatory detrimental effects in the adipose tissue (La Merrill et al.,
303 2013). Organometallic compounds such as tributyltin (TBT), a powerful biocide used in marine shipping
304 applications or as fungicides for paper mills and industrial water systems have also been classified as obesogenic
305 POPs (Grun et al., 2006). Since organotins are now banned, they have been replaced by phenylsulfamides whose
306 effects can be deleterious as shown with tolylfluanid (TF) which can bioaccumulate in adipose tissues (Neel et
307 al., 2013). Other chemicals of very high concern may not be persistent and lipophilic and therefore will not (or
308 little) bioaccumulate in the body. However, due to their massive production especially in the plastics industry
309 and their use for many aspects of modern life, they are ubiquitous in the environment resulting in chronic
310 exposure. It includes plasticizers such as bisphenols and phthalates which impart shape and flexibility to plastic
311 products. Food is the main route of exposure and contamination results from chemical leaching of food and
312 beverage containers and packaging (Koch and Calafat, 2009, Vandenberg et al., 2007).

313 Evidences from experimental studies in rodents have established strong associations between exposure to
314 chemicals, and obesity-related metabolic dysfunction and NAFLD, triggering glucose intolerance and insulin
315 resistance by interacting with various nuclear receptors including steroid receptors, but also peroxisome
316 proliferator-activated receptor and xenobiotic receptors (Diamanti-Kandarakis et al., 2009, Delfosse et al., 2015b,
317 Casals-Casas and Desvergne, 2011, Le Magueresse-Battistoni et al., 2015, Gore et al., 2015). For example, dioxins
318 (a large family of which 2,3,7,8-tetrachlorodibenzo-p-dioxin is the most potent) and dioxin-like PCBs (also called
319 co-planar PCBs) mediate their effects through activating the aryl hydrocarbon receptor (AHR). Interestingly, AHR
320 activation caused hepatic steatosis in male mice fed a high-fat diet (Duval et al., 2017) while male mice deficient
321 for AHR are resistant to diet-induced body weight gain, steatosis and inflammation (Xu et al., 2015). Non-coplanar
322 PCBs (i.e., non-dioxin-like PCBs) do not activate AHR but PXR and CAR, two other xenobiotic receptors involved
323 in liver energy metabolism. In addition, dioxins and PCBs interact with the estrogen and thyroid signaling
324 pathways (Pavek, 2016, Diamanti-Kandarakis et al., 2009, Casals-Casas and Desvergne, 2011). TBT is a strong
325 obesogen interacting with PPAR γ the master regulator of adipogenesis (Rosen and MacDougald, 2006) and RXR α

326 to induce the differentiation of adipocytes as well with estrogen and glucocorticoid signaling mechanisms (Grun
327 and Blumberg, 2006). Early life exposure triggers the reprogramming of the mouse adipocyte stem cells to
328 promote the adipocyte lineage in the subsequent and non-exposed male and female generations, highlighting
329 the transgenerational and epigenetic effects of TBT that caused hepatic steatosis (Egusquiza and Blumberg,
330 2020). PPAR γ can also be activated by phthalates. In addition to being reprotoxic, diethylhexylphthalate (DEHP)
331 and its metabolite mono (2-ethylhexylphthalate (MEHP) exert adverse effects on energy balance and glucose
332 homeostasis by activating PPARs, in particular PPAR γ in adipocytes and PPAR α in the liver with species
333 differences in expression and function (Feige et al., 2007). Phtalates are also antiandrogenic and can activate
334 glucocorticoid receptors (GR) which in addition to PPAR activation may contribute to the development of obesity
335 (Sargis et al., 2010, Casals-Casas and Desvergne, 2011, Wassenaar and Legler, 2017, Schmidt et al., 2012,
336 Benjamin et al., 2017). TF exposure of adult male mice can also induce activation of GR and enhanced body
337 weight, lipogenesis and subsequent glucose intolerance and insulin resistance (Regnier et al., 2015, Neel et al.,
338 2013). Estrogenic EDCs such as BPA conveyed metabolic disruption through complex activation and/or
339 interaction with a large number of nuclear receptors including all three estrogen receptors but also GR, PPAR γ
340 (although in a weak manner) and thyroid receptors, all intricately linked to metabolic health and body weight
341 (Zoeller et al., 2005, Vandenberg, 2009, Nadal et al., 2018, Le Magueresse-Battistoni et al., 2018a). Interestingly,
342 a recent study highlighted that BPA directly mediated its metabolic effects through interacting with ER β in
343 pancreas (Boronat-Belda et al., 2020). In this study, a KO model for ER β (BERKO) was used to describe that ER β
344 was involved in the multigenerational effect of BPA, treating heterozygous BERKO mothers with BPA.

345 International agencies, such as the U.S. Environmental Protection Agency (EPA) or the European Food Safety
346 Agency (EFSA) in charge of human health risk assessment establish toxicological reference values such as
347 reference doses (RfD) and tolerable daily intake doses (TDIs), respectively which are derived from the low or no
348 observed adverse effect levels (LOAELs/NOAELs) determined in experimental studies (Dorne, 2010). However,
349 several reports indicated that the risk assessment would not be sufficiently protective (Kassotis et al., 2020) and
350 should be reconsidered as was done in Europe in 2015, with BPA whose TDI dropped from 50 to 4 μg / kg body
351 weight / day (Bolognesi et al., 2015, Beausoleil et al., 2018). It was motivated by academic results showing
352 adverse health effects of BPA in rodents exposed to the TDI of 50 $\mu\text{g}/\text{kg}$ body weight/day (Vandenberg, 2009, Le
353 Magueresse-Battistoni et al., 2018a). Another concern relates to the difficulty of assessing the cumulative effects
354 of complex mixtures of pollutants on human health: in particular, exposure over a life time to individual chemicals
355 present in a mixture, each at levels below the toxicological reference doses but whose interaction could have
356 distinct effects from those caused by each individual chemical absorbed separately (Le Magueresse-Battistoni et
357 al., 2018b, Kortenkamp, 2014, Delfosse et al., 2015a, Lukowicz et al., 2018a, Le Magueresse-Battistoni et al.,
358 2017). Timing of exposure is also an important parameter to consider. For example, early life exposure could
359 cause metabolic disturbances later in adulthood, referred to as developmental origins of health and disease
360 (DOHaD) and is based on not fully determined epigenetic mechanisms (Barouki et al., 2012, Barker et al., 2002,
361 Grun and Blumberg, 2007).

362 **5.2. EDCs and sex-dimorphic effects on the liver**

363 Various EDCs can cause sex-dependent metabolic disturbances through modifying the pattern of expression of
364 the molecular determinants of sexual dimorphism in the liver as summarized in Table 1.

365 **5.2.1. Metabolic disruptors that alter estrogen signaling pathways in a sex-dimorphic pattern**

366 Ilagan and colleagues (Ilagan et al., 2017) demonstrated that gestational exposure to BPA resulted in increased
367 hepatic expression of ER α and ER β in the female offspring while males showed decrease in expression of both
368 ER α and ER β , in the liver at adulthood. It was accompanied by changes in the pattern of expression of estrogen
369 responsive genes in the liver leading to lasting changes in hepatic glucose and lipid metabolism in adults, in a sex-
370 dependent pattern (Ilagan et al., 2017), which indicated a sex-dependent change of programming in liver in *in*

371 *utero*-treated animals. Increased expression of ER α was also detected in the liver of ovariectomized female mice
372 after a life-time exposure to a mixture of low-dose pollutants including BPA, DEHP, PCB153 and TCDD. These
373 females showed alleviated glucose tolerance and reduced expression of inflammatory markers in WAT providing
374 evidences that the mixture exhibited positive estrogeno-mimetic effects (Julien et al., 2018). In contrast, intact
375 female mice exposed during a lifetime to the same low-dose mixture of pollutants showed reduced expression
376 of ER α and of certain estrogen target genes as well as a marked deterioration of glucose tolerance which may be
377 related to the 2-fold induction of estrogen sulfotransferase. Exposed male siblings did not show changes in
378 glucose tolerance but modifications of cholesterol metabolism (Naville et al., 2013). The results on females are
379 consistent with the literature showing that female mice deficient in EST showed increased estrogenic activity in
380 the liver (Gao et al., 2012) and that estrogens protect females from metabolic-related diseases within a
381 physiological window of estrogen concentrations (Mauvais-Jarvis, 2015). Therefore, it may explain that excess
382 estrogen-mimetic activity carried by the pollutant mixture had triggered adverse effects on glucose tolerance
383 and hepatic insulin sensitivity in adult females, but not in immature or ovariectomized females, nor in males
384 consistent with previous reports (Naville et al., 2013, Naville et al., 2015, Julien et al., 2018). Recently, it has been
385 demonstrated that environmental exposure of BPA could convert lipid metabolism of male zebrafish into a
386 female pattern one. They can accumulate more lipid, especially in liver and WAT prior to gonad feminization.
387 These feminizing events were reproduced using 17 β -estradiol (E2) indicating that the mechanisms operated in
388 the liver through estrogen-dependent signaling pathways (Sun et al., 2020).

389 5.2.2. Metabolic disruptors that alter GH signaling pathways in a sex-dimorphic pattern

390 A recent study (Katz et al., 2020) reported that early life exposure of mice to TBT enhanced adiposity in both
391 male and female mice (although with a different kinetics depending on sex) and caused hepatic tumor formation
392 in males but not in females. The tumors induced by TBT were diagnosed as hepatic adenomas. However, although
393 TBT led to steatosis in males and not in females, TG content did not correlate with development of liver tumors.
394 Indeed, control female liver contained twice higher lipid content than TBT-exposed males and did not develop
395 tumors. Importantly, tumor formation was preceded by alteration of GH signaling with reduced expression of
396 GHR and STAT5 and of target genes such as the major urinary proteins (MUPs). Interestingly, in human studies,
397 GHR is downregulated in HCC, which may indicate an environmental origin in the development of HCC and a
398 gender bias because men are more likely to develop HCC than women (Hoenerhoff et al., 2011). Moreover,
399 analysis of the liver of juvenile male and female mice exposed to TCDD revealed that TCDD repressed male-
400 specific genes while female-specific genes were induced in males and vice-versa (Nault et al., 2017). Disruption
401 of GH-JAK2-STAT5 signaling and inhibition of female specific CUX2-mediated transcription were evidenced
402 although effects were more pronounced in males than in females. Besides, as most genes targeted by TCDD
403 showed dioxin responsive elements (DREs) in promoters it suggested that the TCDD-induced loss of sex
404 dimorphism in the liver was mediated through direct *Ahr*-DRE-dependent regulation (Nault et al., 2017).
405 Decreased GH-JAK2-STAT5 signaling and of GH-responsive genes was as well described in wildtype but not AhR
406 KO male mice, following AhR activation by an AhR agonist (3-methylcholanthrene) (Nukaya et al., 2004).
407 Therefore, it would be interesting to determine whether the adverse effects observed in mice exposed to various
408 EDCs such as BPA, DEHP and dioxins (van Esterik et al., 2015, Duval et al., 2017, Strakovsky et al., 2015, Maranghi
409 et al., 2010) are as well linked to dysregulation of GH signaling.

410 Disruption of the GH-STAT5B pathway has also been described in xenobiotic receptor CAR KO male mice with
411 aging (Lukowicz et al., 2019). Metabolic features of CAR^{-/-} male mice included hepatic steatosis, glucose
412 intolerance and insulin resistance which were not described in CAR^{-/-} female mice unless ovariectomized
413 indicating a protecting role of estrogens. A sexually dimorphic role of CAR was also evidenced in mice exposed
414 to a low-dose cocktail of pesticides (Lukowicz et al., 2018b). Indeed, exposure led to a high death rate in CAR^{-/-}
415 females which was not observed in wild-type female mice or in CAR^{-/-} males. It indicated that CAR expression in
416 females is needed to cope with exposure to CAR-activating pollutants. Whether it is related to the estrogenic
417 regulation of CYP2B10 (Yamada et al., 2002), the prototypical gene of CAR activation warrants further study.

418 Moreover, while exposure to the cocktail of pesticides led to obesogenic effects in wild type males, wild-type
419 female mice exhibited fasting hyperglycaemia indicating diabetogenic effects (Lukowicz et al., 2018b).

420 5.2.3. Metabolic disruptors that alter GR signaling pathways in a sex-dimorphic pattern

421 Glucocorticoids (GCs) play a central role in metabolic programming. The adipose tissues and the liver are major
422 metabolic tissues targeted by GCs (Lee et al., 2018, Vegiopoulos and Herzig, 2007). Interestingly early life
423 exposure to tolylfluanid (TF) a GR agonist was found to induce sex-specific later-life metabolic dysfunction (Ruiz
424 et al., 2019). Female mice showed enhanced systemic insulin sensitivity, reduced adiposity and normal hepatic
425 gluconeogenic activities while males had impaired glucose tolerance and no changes of adiposity. Mechanistic
426 basis leading to mis-programming of metabolism are probably epigenetic and possibly the consequences of
427 primary GC effect on dams (Ruiz et al., 2020). Indeed, males exposed during adulthood showed enhanced body
428 weight, adiposity and insulin resistance (Regnier et al., 2015). Studying the effects of TF exposure in adult female
429 mice will allow determining if sex-specific effects also occurred during adulthood. In addition, it would be
430 interesting to measure the hepatic and adipose levels of expression of glucocorticoid receptors (GR),
431 mineralocorticoid receptors (MR) and 11 β HSD1. Indeed, these genes are identified targets of endocrine
432 disruptors (Vega et al., 2020), and liver knockdown of 11 β HSD1 which allows local amplification of GCs in the
433 absence of variations in plasma corticosterone levels (Lee and Fried, 2014), reduced lipid synthesis and
434 accumulation protecting from Western type diet-induced steatosis (Li et al., 2011).

435 5.2.4. Metabolic disruptors that alter microbiota and the gut-liver axis and potential sex-differences

436 Interestingly, in light of the critical role played by the gut microbiota in the development and progression of
437 NAFLD via the gut-liver axis (Tilg et al., 2016), it has been shown that the altered ability of the gut microbiota to
438 metabolize tryptophan into AHR agonists was associated with components of the metabolic syndrome, in mice
439 and humans. Moreover, in this study (Natividad et al., 2018), restoration of AHR signaling via supplementation
440 with AHR agonist or a *Lactobacillus* strain naturally producing AHR ligands could alleviate both gut permeability
441 and metabolic syndrome in mice. Thus, TCDD and TCDD-like compounds which bind AHR can inappropriately
442 activate AHR signaling causing gut microbiota alterations. Interestingly, exposure of male mice to TCDD or TCDD-
443 like compounds would mediate hepatotoxicity through mechanisms involving gut microbiota-host metabolic
444 homeostasis, bile acid homeostasis and entero-hepatic circulation (Fader et al., 2017) interfering with the
445 circadian regulation of hepatic metabolic activity in mice (Fader et al., 2019). It has been reported that endocrine
446 disruptors could alter the expression of hepatic circadian gene expression in rodent exposure models (Labaronne
447 et al., 2017, Antherieu et al., 2014). Furthermore and in line with the findings of Fader and colleagues, Gachon
448 and colleagues have proposed that the reciprocal interactions between the host circadian clock and the
449 microbiota could be associated with impaired GH secretion (Weger et al., 2019b) and therefore would show sex
450 dimorphism. Therefore, it would be of great interest to explore if supplementation with AHR agonists or a
451 *Lactobacillus* strain as described elsewhere (Natividad et al., 2018), could mitigate the phenotype described in
452 males exposed to TCDD in the study of Fader and colleagues (Fader et al., 2017) and to explore females.
453 Unfortunately, female gut microbiota were not explored in the study because females have shown less
454 susceptibility to hepatotoxicity caused by TCDD than males (Fader et al., 2017).

455 Interventional studies could also be developed in female mice exposed to various PCB congeners, including
456 PCB126, a dioxin-like PCB, where specific bacterial taxa have been positively linked to dyslipidemia and NAFLD
457 (Chi et al., 2019). Other studies reported that male mice exposure to BPA, DDE and phthalates could trigger
458 changes in gut microbiota composition and diversity. Specifically, mice post-natally exposed to BPA in the range
459 of the TDI dose showed reduced diversity and altered composition of the gut microbiota such as reduced
460 abundance of *Akkermansia* associated with alterations in the permeability of the intestinal barrier and hepatic
461 steatosis. Interestingly, body weight did not change (Feng et al., 2020) indicating that dysbiosis was not related
462 to obesity but possibly to alterations in the gut-liver axis. Perinatal exposure to the same dose of BPA also caused
463 intestinal dysbiosis with a decrease of *Bifidobacteria* and inflammation of the liver in young adult male mice in a

464 way that preceded the obesity shown with older mice (Malaise et al., 2017). Male mice prenatally exposed to
465 DEHP showed as well gut microbiome dysbiosis dominated by *Bacteroidetes* and *Firmicutes* along with enhanced
466 body weight, dyslipidemia and steatosis but the kinetics in the appearance of the metabolic disorders was not
467 explored (Fan et al., 2020). An increased *Firmicutes-to-Bacteroidetes* ratio which characterized gut dysbiosis in
468 obese conditions was also described in male rats treated with DDE along with enhanced body weight and
469 alterations of the plasma lipid metabolome profile but the hepatic function was not explored. In particular,
470 phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine and triacylglycerol were identified as key
471 metabolites affected by DDE treatment which levels highly correlated with changed microbiota composition
472 (Liang et al., 2020). However, it has not been studied whether these adverse effects on the microbiota could also
473 be described in female mice exposed to BPA, DDE or phthalates. Likewise, the question of whether tryptophan
474 metabolites could be potential targets of endocrine disruptors in the gut microbiota of mice has not been
475 investigated.

476 6. Conclusions and future directions

477 Over the past 20 years, the evidence that endocrine disruptors are etiological factors in the pandemic course of
478 obesity and diabetes mellitus, hepatic steatosis and NAFLD and other associated metabolic disorders has grown
479 considerably, as reviewed here. However, most studies have been performed with male individuals although the
480 National Institutes of Health (NIH) since 1990, and more recently, the WHO and the European Commission have
481 included gender equality as a criterion of scientific excellence (Liu and Mager, 2016, Gahagan et al., 2015).
482 Therefore, it is necessary to systematically include female individuals in the experimental protocols to enhance
483 our understanding on how females cope with environmental exposure to chemicals and to test both normal and
484 unbalanced nutritional conditions, such as a high-fat high in sugar regimen typical of the Western type diet.
485 Indeed, women still represent only 30% of participants in clinical trials, weakening the evidence base for women.
486 Yet a woman who takes a drug is almost twice as likely as a man to experience side effects (Khan et al., 2020).
487 Hopefully, in the near future clinical trials will incorporate more women and of different ages because the
488 reproductive period represents on average one third of a woman's life, which is equivalent to the menopausal
489 and postmenopausal transition period. It means that the protection conferred by estrogens concerns only part
490 of a woman's life. This will help to better understand the onset and progression of sex-related liver disease,
491 particularly how sex hormones influence liver inflammation and disease progression.

492 Care should also be taken to use female cell lines in the in vitro mechanistic studies. Interestingly, the human
493 HepaRG cell line has been derived from the tumor of a female patient suffering from hepatitis virus infection. It
494 is physiologically one of the closest cell lines to the primary human hepatocyte because this established hepatic
495 cell system is able to produce early hepatic progenitor cells as well as completely mature human hepatocytes
496 (Gripone et al., 2002). In addition, HepaRG has already proved useful for developing an in vitro model of steatosis
497 and insulin resistance (Le Guillou et al., 2018, Bucher et al., 2018). The omics approaches of HepaRG exposed to
498 various EDCs or low-dose mixtures of EDCs under (or not) steatotic conditions (Legler et al., 2020) should inform
499 on EDCs modes of action and sex-specificities. It would help complete the initiatives of the Organization for
500 Economic Development (OECD) on Adverse Outcome Pathways (AOPs) (Gourmelon, 2018).

501 As industrialization will go up, the list of anthropogenic chemicals to which humans will be exposed will probably
502 as well grow up. Hopefully strengthening existing regulations and encouraging substitution of harmful chemicals
503 will limit human exposure, although substitution is a difficult task as seen with bisphenol analogues to replace
504 BPA ultimately reported as unsafe chemicals (Serra et al., 2019, Thoene et al., 2020). Populations must also be
505 encouraged to reduce their own exposure to endocrine disruptors through a display and information policy. In
506 addition, the microbiota and the intestine-liver axis open up new and vast perspectives in the field of endocrine
507 disruptors. For example, by targeting factors derived from the gut microbiota and relevant host cell signaling,
508 one can imagine new intervention strategies for NAFLD such as nutritional intervention with prebiotics or
509 probiotics to counteract the deleterious metabolic effects of pollutants as performed in obese patients to
510 improve metabolic parameters (Roca-Saavedra et al., 2018, Depommier et al., 2019) and experimentally to

511 restore AHR signaling (Natividad et al., 2018) or maintain growth during chronic undernutrition (Schwarzer et al.,
512 2016). This could make it possible to remedy the deleterious effects of pollutants in a manner, if not personalized,
513 at least according to sex and developmental age, for the benefit of the health of both women and men.

514

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518

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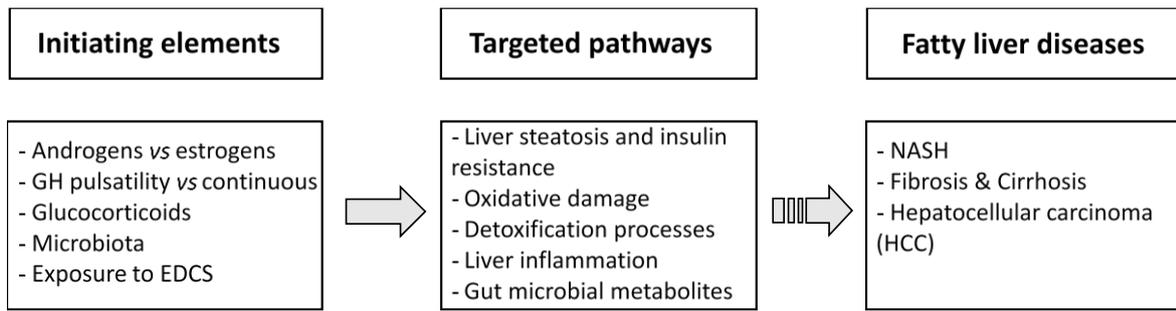
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1007 **Figure 1:** Various initiating elements which depend on sex (apart from exposure to EDCs) can trigger several
1008 targeted pathways whose deregulation could lead to the development of fatty liver diseases.



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1013 **Table 2:** Summary of the main effects of EDCs on the signaling pathways initiated by sex steroids, GH,
 1014 glucocorticoids, and on microbiota. Several characteristics are provided such as the animal model, the route of
 1015 exposure, dosage and timing, the outcomes measured as well as the conclusions of the authors, and the
 1016 references.

Table1:

Animal model	EDC	Route of exposure and dosage	Timing of exposure	End-points measured	Sex	Conclusions of the authors	Re
Metabolic disruptors that alter estrogen signaling pathways							
Pregnant CD-1 mice	BPA	5 mg/kg body weight (bw)/day (d) or DMSO via osmotic mini-pump	Days 9-18 of gestation	Analysis of the hepatic transcriptome of 8-week old mice treated for 6h with estradiol (300 ng, IP) or vehicle (DMSO)	Both males and females (ovariectomized by 6 weeks)	BPA exposure in utero caused hepatic gene changes that lasted in adulthood and programmed a sexually dimorphic estrogenic state	lla al.
C57BL6J mice	Mixture of BPA, DEHP, PCB153 and TCDD	Doses in the TDI range (BPA: 5 µg, DEHP: 50 µg, PCB153 80 ng, TCDD 2 pg (all/kg bw/d) mixed in a high-fat high-sucrose (HFHS) diet	Lifelong starting 5 weeks before mating until female offspring (F1) reached 12 weeks of age	Comparison of the metabolic phenotype of sham versus ovariectomized F1 (surgery in 5-week-old mice)	Females (F1 generation)	The mixture of BPA, DEHP, PCB153, TCDD exerted estrogeno-mimetic effects in liver and adipose tissues	Ju al.
C57BL6J mice	Mixture of BPA, DEHP, PCB153 and TCDD	Doses in the TDI range (BPA: 5 µg, DEHP: 50 µg, PCB153 80 ng, TCDD 2 pg (all/kg bw/d) mixed in a high-fat high-sucrose (HFHS) diet	Lifelong starting 5 weeks before mating until offspring (F1) reached 12 weeks of age	Analysis of the metabolic phenotype of the male and female offspring (adult stage)	Both males and females (F1 generation)	Females showed aggravation of glucose intolerance associated with reduced estrogenic signaling in the liver. Males did not show changes in glucose tolerance but cholesterol modifications.	Na al.
C57BL6J mice	Mixture of BPA, DEHP, PCB153 and TCDD	Doses in the TDI range (BPA: 5 µg, DEHP: 50 µg, PCB153 80 ng, TCDD 2 pg (all/kg bw/d) mixed in a high-fat high-sucrose (HFHS) diet	Lifelong starting 5 weeks before mating until female offspring (F1) reached 6 weeks of age	Analysis of the metabolic phenotype of the female offspring (juvenile stage)	Both males and females (F1 generation)	Females showed attenuation of the high fat diet-induced obesity characterized by attenuation of glucose intolerance, enhanced insulin signaling (significant in muscles), enhanced lean/fat mass ratio and reduced inflammatory markers in the adipose tissue. Pollutant-exposed males showed no changes vs unexposed males.	Na al.
AB strain of adult zebrafish	BPA	BPA (100µg/l) or E2 (200ng/L); the estrogen receptor antagonist Tamoxifen was also used	Both male and female adults were exposed for 6 weeks into 30 L glass tanks with normal-, low- or high- fat diet	Lipid content (total, liver and muscles) plus hepatic transcriptomic analyses	Both males and females	BPA exposure converts lipid metabolism in male fish to a female pattern; metabolic feminization of the liver precedes gonad feminization in male fish	Su 2C
Metabolic disruptors that alter GH signaling pathways							
C57BL6J mice	TBT	TBT (0.5 mg/kg bw/d (3.07 µM) via drinking water	Exposure of dams from pre-conception through lactation	Analysis of adiposity, hepatic steatosis and tumor development in 14, 20 and 45 weeks of age.	Both males and females of the F1 generation	Female offspring showed increased adiposity versus males but TBT did not trigger enhanced fatty liver or tumor development. Males showed liver tumors which development was preceded with decreased GHR and STAT5 signaling.	I al.
C57BL6J mice	TCDD	Oral gavage with 0.1 ml of sesame oil containing 0.01, 0.03, 0.3, 1, 3, 10 and 30 µg/kg bw	Exposure started on post-natal day 28 and every following 4th day for 28 d in males and 92 d in females	RNA-seq in liver	Both males and females	TCDD resulted in loss of sexually dimorphic gene expression in males with diminished divergence between sexes. Disrupted regulation in males is consistent with impaired GHR-JAK2-STAT5 signaling, concurrently with the induction of alpha-foetoprotein typically associated with HCC or liver regeneration. These latter effects were not described in females.	I al.
C57BL6J mice	3-Methylcholanthrene (3-MC)	3-MC dissolved in corn oil at a dose of 80 mg/kg bw/d; Intraperitoneally injection (IP).	treatment of 8-week old mice once daily for 2 days	Liver transcriptomic analysis by differential mRNA display and comparison with AhR KO mice	Only males were studied	Decreased expression of GH receptor and of downstream components of the GH signaling pathway and GH-responsive genes, events which were not observed in AhR KO mice	I al.
C57BL6J mice	mixture of ziram, thiophanate, captan, chlorpyrifos, boscalid, thiachlorpride	Pesticides were incorporated in the rodent pellet diet assuming a bw of 30 g and a daily food intake of 5 g for all mice to achieve a daily exposure at the TDI of each pesticide	Exposure from 1-weeks of age for a total of 52 weeks	Analysis of metabolic parameters and liver metabolism (histology, transcriptomics, metabolomics, lipidomics); comparison with CAR KO mice	Both males and females	Males exposed to pesticides showed enhanced bw, glucose intolerance and hepatic steatosis, not described in CAR KO males exposed to pesticides vs unexposed CAR KO males. Females exposed to pesticides showed hyperglycaemia but no changes in bw or hepatic steatosis (shown in males). However, CAR KO females treated with pesticides showed higher bw and mortality compared to CAR KO females fed a control chow diet. These data point to obesogenic and diabetogenic effects of the mixture of pesticides in males and females, respectively.	I al.
Metabolic disruptors that alter GR signaling pathways							
C57BL6J mice	Tolyfluand (TF)	67 mg/kg in standard rodent chow diet	Exposure throughout pregnancy and lactation	Metabolic phenotyping including metabolic tests	Both males and females (F1) up to 22 weeks of age	In response to a maternal exposure to TF, females showed reduced bw while males showed no changes of adiposity; females had normal hepatic neoglucogenesis while males showed impaired glucose tolerance; females but not males showed increased whole-body insulin sensitivity.	I al.

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C57BL6J mice	Tolyfluanid (TF)	Standard chow diet supplemented or not with 100 ppm of TF added at the time of manufacturing	12-week exposure period starting with 8-week old mice	Metabolic phenotyping including metabolic tests	Only males	TF-treated males showed enhanced body weight and adiposity, glucose intolerance and insulin resistance, as well as disrupted adipokine profile and enhanced GR signaling in the adipose tissue.
C57BL6J mice	Mixture of BPA, DEHP, PCB153 and TCDD	BPA: 40 µg, DEHP: 500 µg, PCB153 200 ng, TCDD 20 pg (all/kg bw/d) mixed in standard (ST) or a high-fat high-sucrose (HFHS) diet	16-week exposure period starting with mice of 4 weeks of age	Analysis of the metabolic phenotype of the female offspring (juvenile stage)	Both males and females	Females exposed to the mixture showed reduced leptin levels and reduced mRNA levels of the corticoid receptors GR and MR and of 11b-HSD1 in the visceral but not the subcutaneous adipose tissue. Males exposed to the same mixture did not show reduced leptin levels. GR, MR and 11b-HSD1 mRNA levels did not change in male and female liver in response to the mixture.
Metabolic disruptors that alter gut microbiota						
C57BL6 mice	TCDD	30 µg/kg bw TCDD in sesame oil; oral gavage at Zeitgeber time (ZT) 0	Every 4 days for a total of 7 exposures	Histopathology, RNA-Seq analysis, CHIP and putative DRE identification, Bile acids composition, intestinal function and microbiota	Only males	TCDD-treated male mice showed increased bile acid (BA) levels in liver and serum in line with hepatic accumulation of cholesterol. BA-induced feedback inhibition was disrupted. Enterohepatic circulation and transport were impaired with a significant decrease of fecal BAs suggesting increases in gut transit time and intestinal permeability. There are also evidences of alterations in host and BA metabolism.
C57BL6 mice	PCB126	50 µg/kg bw PCB126 in corn oil; oral gavage of adult mice	Treatment duration of 6 weeks	Liver histopathology, biochemical assay and gut microbiota composition analysis	Only females	Females exposed to PCB126 showed dyslipidemia, liver lipid accumulation, and NAFLD; as well as changes in gut microbiota composition. Several Spearman's correlation analysis indicated that several specific bacterial taxa were positively associated with metabolic disorders.
CD-1 mice	BPA	BPA was incorporated in control chow diet at 0.5 mg/kg of food considering that daily diet accounts for 10% of the body weight per day, this was equivalent to oral exposure of 50 µg/kg bw /d; vehicle: soy oil	24-week exposure starting with 6 week-old mice	Biochemical assay, histology, gene expression and gut microbiota analyses	Only males	BPA-treated males showed hepatic lipid accumulation. Analysis of 16S revealed reduced diversity of gut microbiota and altered composition. Expression levels of markers of intestinal permeability decreased leading to increased permeability and elevated levels of endotoxins, and increased liver inflammation (interleukins 1β and 6, TNFα).
C3H/HeN	BPA	Daily oral administration of 50 µg/kg bw BPA in corn oil	from gestation day 15 to weaning of the offspring	Metabolic tests; antimicrobial and Lysozyme activity; determination of faecal microbial communities and flow cytometry.	Only males (F1 offspring)	BPA-treated males showed intestinal and systemic immune imbalance at PND45 associated with altered glucose tolerance, a defect in IgA secretion into faeces and a drop in faecal bifidobacteria relative to control mice. These BPA-mediated events preceded obesity development, insulin resistance and inflammation in the adipose tissue observed in aging male mice (PND125).
ICR mice	DEHP	0.2, 2 and 20 mg/kg bw/d in DMSO by daily oral gavage	Duration of treatment included 1 week pre-mating and gestation (3 weeks)	Body composition and serum lipid, metabolomic, hepatic gene expression and gut microbiota profiling of 12 week-old mice.	Both males and females	Prenatal exposure to the low dose (not the higher doses) induced an increase in body weight in males only, with no change in food intake. Females have not been studied further. Decrease in overall energy expenditure, dyslipidemia, steatosis and hepatic thiamine deficiency were described as well as gut dysbiosis. These changes appear to be predominantly related to changes in liver metabolism not by alterations of the gut microbiome.
Sprague-Dawley rats	DDE	Gavage of four-week old rats at a daily dose of 2 mg/kg bw in corn oil	Treatment duration of 21 days	Glucose homeostasis, analysis of gut microbiota and lipidomic profile	Only males	DDE-treated males showed enhanced body weight and fat content, impaired glucose tolerance and insulin resistance. DDE caused large changes in gut microbiota, especially in the proportion of <i>Firmicutes</i> (increased), <i>Bacteroidetes</i> (decreased) and others (<i>Tenericutes</i> , <i>Proteobacteria</i> , <i>Prevotellaceae</i>). Plasma lipid profiles were altered and the altered lipid metabolites correlated with the altered microbiota and metabolic disorders.

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