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Effects of endocrine disrupting chemicals on myelin development and diseases

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1 **TITLE**

2 **Effects of endocrine disrupting chemicals on myelin development and diseases**

3

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27 **ABSTRACT**

28 In the central and peripheral nervous systems, myelin is essential for efficient conduction of action
29 potentials. During development, oligodendrocytes and Schwann cells differentiate and ensure axon
30 myelination, and disruption of these processes can contribute to neurodevelopmental disorders. In
31 adults, demyelination can lead to important disabilities, and recovery capacities by remyelination
32 often decrease with disease progression. Among environmental chemical pollutants, endocrine
33 disrupting chemicals (EDCs) are of major concern for human health and are notably suspected to
34 participate in neurodevelopmental and neurodegenerative diseases. In this review, we have
35 combined the current knowledge on EDCs impacts on myelin including several persistent organic
36 pollutants, bisphenol A, triclosan, heavy metals, pesticides, and nicotine. Besides, we presented
37 several other endocrine modulators, including pharmaceuticals and the phytoestrogen genistein,
38 some of which are candidates for treating demyelinating conditions but could also be deleterious as
39 contaminants. The direct impacts of EDCs on myelinating cells were considered as well as their
40 indirect consequences on myelin, particularly on immune mechanisms associated with
41 demyelinating conditions. More studies are needed to describe the effects of these compounds and
42 to further understand the underlying mechanisms in relation to the potential for endocrine
43 disruption.

44

45 **Keywords:** myelin, oligodendrocyte, Schwann cell, endocrine disrupting chemical, hypomyelination,
46 demyelination

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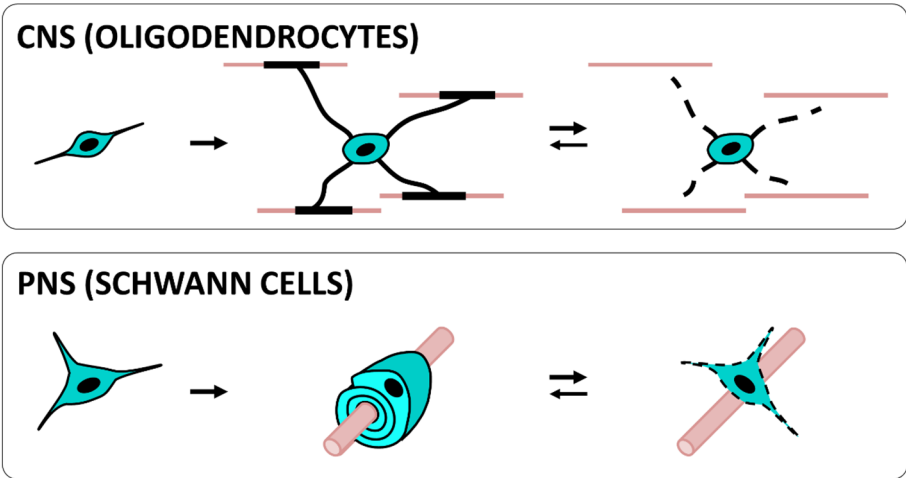
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57 **GRAPHICAL ABSTRACT**

ENDOCRINE DISRUPTING CHEMICALS
persistent organic pollutants, bisphenol A, heavy metals...



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61 **HIGHLIGHTS**

- 62 • Endocrine signals play a crucial role in myelin development and diseases.
- 63 • Several EDCs can interfere with myelination during development.
- 64 • Several EDCs exert deleterious effects on myelin in the mature nervous system.
- 65 • Some endocrine modulators could be therapeutic options in demyelinating conditions.
- 66 • The underlying mechanisms of EDCs impacts on myelin are still poorly understood.

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107 **1. Introduction**

108 Myelin is a lipid-rich sheath surrounding axons that ensures rapid conduction of electric signals, thus
109 allowing efficient neural communication and normal neurological function. In addition, myelin plays
110 other crucial functions such as physical protection and metabolic support of axons (Stadelmann *et*
111 *al.*, 2019). In the central nervous system (CNS), myelin is formed by oligodendrocytes (OLs) whereas
112 in the peripheral nervous system (PNS), this function is devoted to Schwann cells (SCs). In the CNS,
113 the white matter is mainly composed of myelinated axons (Quarles *et al.*, 2005a). Myelin
114 abnormalities lead to communication defects resulting in neurological deficits. Myelin defects are
115 thus observed in many pathological contexts (Pleasure, 2005; Quarles *et al.*, 2005b; Stadelmann *et*
116 *al.*, 2019). Schematically, two main causes of myelin diseases can be distinguished: i) failure of
117 myelin synthesis during development (dysmyelination) leading to hypomyelination; ii) myelin
118 destruction throughout life, or demyelination, frequently linked to autoimmune mechanisms.
119 Several genetic factors involved in myelin pathologies have been identified. For example, mutations
120 in proteolipid protein 1 (*PLP1*) gene are involved in Pelizaeus-Merzbacher disease, an X-linked
121 congenital white matter disease. Pelizaeus-Merzbacher disease belongs to leukodystrophies, which
122 comprise a group of inherited diseases primarily affecting the CNS white matter (Quarles *et al.*,
123 2005b). Charcot-Marie-Tooth disease is another hereditary dysmyelinating condition which affects
124 peripheral nerves and can be caused by mutations in several genes such as those coding for
125 connexin 32, myelin protein zero (P0, MPZ) and peripheral myelin protein 22 (PMP22) (Pleasure,
126 2005). Concerning demyelinating diseases, specific variations in immune-related genes, for example
127 the major histocompatibility complex, class II, DR beta-1 (*HLA-DRB1*) gene, have been associated
128 with an increased risk of multiple sclerosis (MS) (Harbo *et al.*, 2013). However, in many contexts,
129 myelin pathologies are more likely to result from interactions between genetic and environmental
130 factors. In fact, environmental factors may play a key role in disease etiology, especially when no
131 genetic factor is identified.

132 Environmental stressors are highly diverse and include notably infectious, nutritional, physical and
133 chemical exposures. Among environmental chemical pollutants, endocrine disrupting chemicals
134 (EDCs) are of major concern for human health (Kabir *et al.*, 2015; WHO, 2012). Growing evidence
135 supports a deleterious impact of many EDCs in neurodevelopment and mature nervous system
136 homeostasis (Masuo and Ishido, 2011). Current research is mainly focused on sexually dimorphic
137 brain areas and reproductive behaviors, and, to a lesser extent, other functions including cognitive,
138 emotional, and sensorimotor performances in animal models and clinical studies. In human, early-
139 life exposures to EDCs were notably associated with decreased cognitive performances, impaired

140 social interactions, and attention deficits (Braun, 2017; Grandjean and Landrigan, 2014). In terms of
141 cellular mechanisms of EDC neurotoxicity, alterations of neuronal functions were mainly addressed,
142 whereas glial cells were far less studied. However, glial cells, including myelinating cells, are of
143 growing interest in the field of environmental toxicology (Kraft, 2015). Importantly and as
144 mentioned above, myelin defects were described in many pathological contexts. Furthermore, it is
145 important to note that myelin formation and homeostasis are tightly controlled by extrinsic signals,
146 including hormones (Barateiro *et al.*, 2016). Moreover, hormones can modulate immune responses
147 involved in demyelinating diseases (Kipp and Beyer, 2009; Ysraelit and Correale, 2019). EDCs are
148 therefore likely to disrupt these processes, particularly by mimicking or impairing hormonal effects
149 (Mughal *et al.*, 2018). This review aims to compile current information regarding EDCs impacts on
150 myelin. After presenting essential outlines of myelin biology, we will review the effects of
151 environmental chemical compounds classified as endocrine disruptors, although endocrine
152 disrupting mechanisms were not always addressed regarding myelin impacts.

153

154 **2. Myelin biology**

155 2.1. Myelin structure and composition

156 The myelin sheath consists of compact concentric layers of plasma membrane extensions wrapping
157 around axons in a regularly spaced manner. The multilayered ultrastructure of myelin can be
158 effectively visualized in transmission electron microscopy (TEM) images which reveal a periodic
159 repetition of electron-dense (major dense line) and light (intraperiod line) layers (Stadelmann *et al.*,
160 2019). In the CNS, each OL myelinates up to 40 different axons whereas in the PNS, each SC
161 myelinates a unique axon segment by forming several layers of myelin and a final ring of cell
162 cytoplasm outside the sheath (Garbay *et al.*, 2000; Stadelmann *et al.*, 2019). Myelin segments are
163 separated by unmyelinated segments called Ranvier nodes which concentrate voltage-dependent
164 sodium channels involved in depolarization and action potential propagation. Myelin itself is not an
165 electric conductor, but it accelerates signal conduction by causing the excitation to jump to the next
166 node instead of flowing through unmyelinated fibers (Quarles *et al.*, 2005a).

167 The molecular composition of myelin has been well characterized (Quarles *et al.*, 2005a). Myelin
168 owes its insulating properties to its high lipid content, corresponding approximately to 70 % of its
169 dry weight, with proteins thus representing about 30 % of myelin weight. This composition
170 distinguishes myelin from other plasma membranes in which proteins are at the very least equally as
171 abundant as lipids (Deng and Poretz, 2001a; Quarles *et al.*, 2005a). Moreover, myelin contains higher

172 amounts of galactocerebrosides (galactosylceramides) and sulfatides, particularly in the CNS in
173 which they reflect myelin biosynthesis (Schmitt *et al.*, 2015). Myelin also contains specific proteins.
174 In the CNS, the two major myelin proteins are transmembrane PLP and myelin basic protein (MBP),
175 whereas main proteins of peripheral myelin are MPZ (P0), MBP (at lower levels than in CNS) and
176 PMP22, PLP being expressed only at very low levels in the PNS. Other myelin proteins include
177 notably 2',3'-cyclic nucleotide 3'-phosphodiesterase (CNPase) and transmembrane myelin-associated
178 glycoprotein (MAG), which are expressed both in PNS and CNS, and transmembrane myelin
179 oligodendrocyte glycoprotein (MOG), specifically expressed by OLs (Jahn *et al.*, 2009; Quarles, 2005).

180 Several approaches are classically used to evaluate myelin quantity, quality, and integrity. In clinical
181 studies and some *in vivo* studies, magnetic resonance imaging (MRI) allows visualization of focal and
182 diffuse white matter lesions (Stadelmann *et al.*, 2019). Histological approaches such as TEM are used
183 to analyze the proportion of myelinated axons, myelin compaction and thickness, specifically by
184 calculating the *g-ratio* (ratio of the inner axonal diameter to the total outer diameter of myelinated
185 fiber). Molecular analyses are also performed to determine myelin composition and thus reveal
186 possible deficits in specific components of mature myelin (Quarles, 2005).

187 2.2. Myelin synthesis and plasticity

188 The human CNS takes 20 to 25 years to mature, with the myelination process starting late and
189 continuing over a long duration of time. The whole process of brain development begins at 3-4
190 gestational weeks (gw) with neurulation, corresponding to the formation of the neural tube that will
191 give rise to the CNS. Neurogenesis and morphological formation of brain structures begin shortly
192 after neurulation and are nearly complete at birth. Gliogenesis starts when neurogenesis is almost
193 complete, giving rise to the two major types of macroglial cells, astrocytes and OLs (Jiang and
194 Nardelli, 2016). OL precursor cells (OPCs) arise during the first trimester of gestation between 10 and
195 18 gw from multipotent neuroepithelial progenitors in the ventricular zone (Barateiro *et al.*, 2016).
196 Since neurons and neural glial cells have the same multipotent progenitors, transition from neuron
197 to glia is achieved by switch of developmental programs from neurogenesis to gliogenesis according
198 to a finely regulated spatiotemporal pattern (Jiang and Nardelli, 2016). After specification, OPCs
199 undergo intense proliferation, especially during the second trimester of pregnancy. At the same
200 time, OPCs start to migrate from ventral to dorsal areas of the CNS, with the majority differentiating
201 into late OPCs (or pre-OLs) and few pre-myelinating OLs (or immature OLs). During the third
202 trimester, mature OLs are progressively generated by terminal differentiation, marking the
203 beginning of myelination (Barateiro *et al.*, 2016). In rodents, however, myelination does not start
204 before birth, with the two first postnatal weeks thus corresponding approximately to the third

205 trimester of human pregnancy (Semple *et al.*, 2013). This species-specific time course of myelination
206 is important to remember for designing and interpreting *in vivo* studies. As mentioned above, in
207 human brain, white matter development continues for at least 2 decades (Semple *et al.*, 2013). The
208 progression of OL differentiation can be followed by characterizing the distribution of OL lineage
209 stages using specific markers such as A2B5, platelet-derived growth factor receptor alpha (PDGFR α)
210 and Neural/glial antigen 2 (NG2) for OPCs, O4 and G-protein-coupled receptor 17 (GPR17) for late
211 OPCs (still expressing some OPC markers) and pre-myelinating OLs (starting to express mature OL
212 markers) and finally CNPase, PLP, MBP, MOG and MAG for mature OLs (Fumagalli *et al.*, 2011;
213 Schumacher *et al.*, 2012) (Figure 1).

214 Like most PNS cells, SCs arise from the delamination of neural crest cells at the dorsal margin of the
215 neural tube during early embryogenesis (Castelnovo *et al.*, 2017). In contrast with OLs, SCs are the
216 only neural glial cells of the PNS. From mid-gestation, proliferative and migratory SC precursors
217 undergo differentiation into immature, pro-myelinating and finally mature SCs with two possible
218 fates through the mechanism of radial sorting. In brief, at the vicinity of large diameter axons,
219 mature SCs differentiate into myelinating SCs while non-myelinating SCs embed smaller axons within
220 Remak bundles (Castelnovo *et al.*, 2017). Like OLs, SC differentiation can be followed by studying the
221 expression of specific markers (Macklin and Rasband, 2012). SC precursors notably express N-
222 cadherin (a marker of neural crest cells), cadherin 19 and start to express low levels of MPZ, PLP and
223 PMP22. Immature SCs then transiently express glial fibrillary acidic protein (GFAP) and S100 β , which
224 are maintained in non-myelinating SCs. Finally, maturation into myelinating SCs leads to high
225 expression of myelin proteins (Figure 1).

226 After its formation, myelin continues to display some plasticity with possible modifications in
227 thickness, compaction, distribution along axons, and expression of molecules involved in axonal
228 metabolic support (Chapman and Hill, 2020). However, the predominant feature of myelin plasticity
229 relies on resident OPCs in adult CNS which can differentiate into new myelinating OLs throughout
230 life (Chapman and Hill, 2020). In physiological conditions, this may notably contribute to the
231 replacement of dying OLs to maintain a constant degree of myelination, and the continued
232 myelination of previously unmyelinated fibers during adulthood. Importantly, in demyelinating
233 diseases, the generation of new myelinating cells plays a crucial role in lesion repair capacity by
234 allowing, to some extent, axon remyelination (Bergles and Richardson, 2015). Indeed, OPC
235 proliferation increases in response to acute demyelination in order to generate an adequate number
236 of myelinating OLs, allowing remyelination and functional recovery (Sanchez *et al.*, 2018). However,
237 remyelination becomes less effective with time in chronic demyelinating diseases such as MS,
238 possibly due to inhibitory signals (Chedrawe *et al.*, 2018; Sanchez *et al.*, 2018). In the PNS, myelin

239 plasticity is even more pronounced since mature SCs have the capacity to dedifferentiate into
240 immature cells taking part in lesion repair by participating in axon regeneration and its subsequent
241 myelination (Schumacher *et al.*, 2012).

242 2.3. Extrinsic regulation of myelination: role of hormones

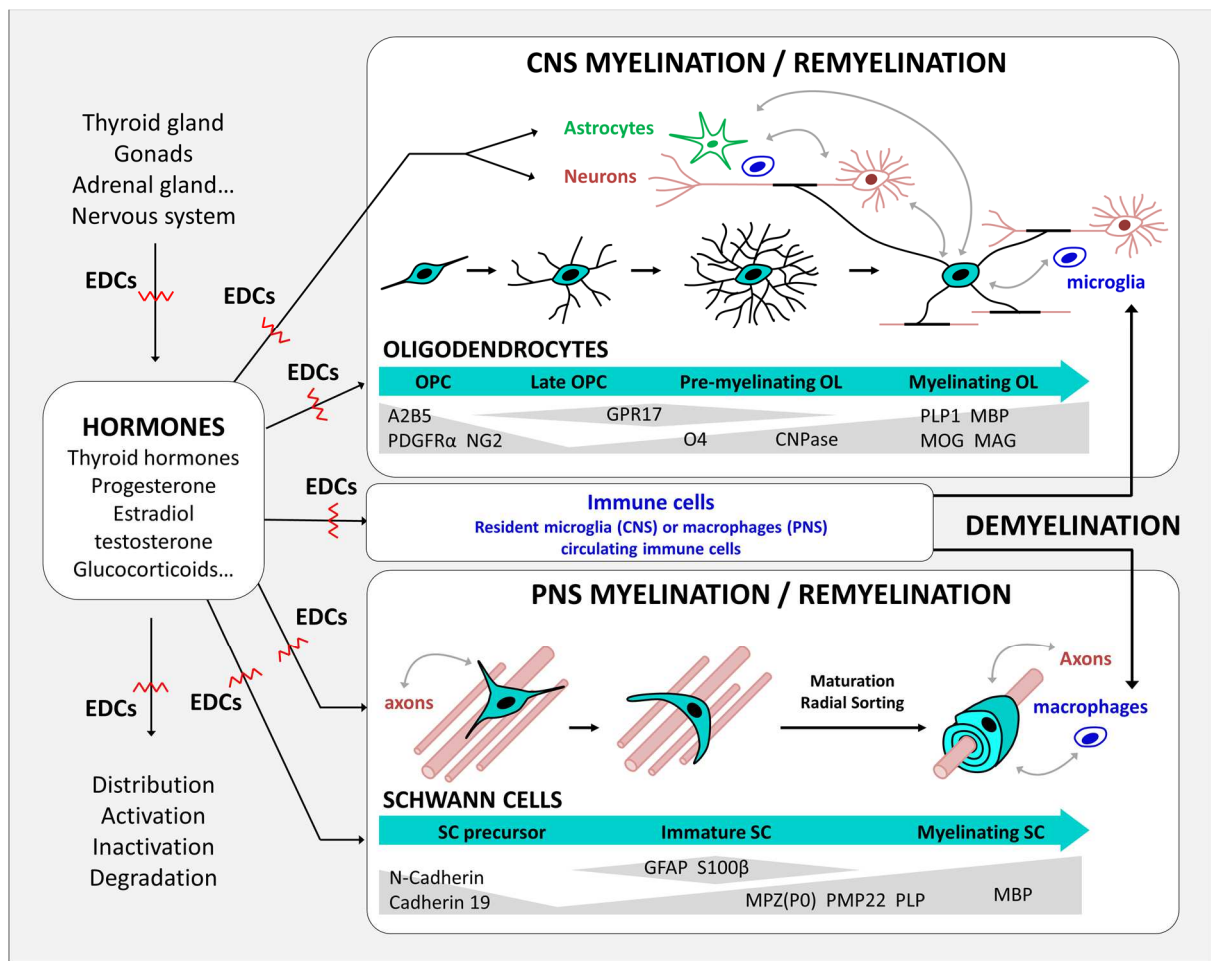
243 During and after myelination, many cell-cell communications take place between neurons and glia
244 including close reciprocal interactions between axons and myelinating cells. Several growth factors
245 regulate myelination through autocrine and paracrine mechanisms. For example, neurons and
246 astrocytes secrete platelet-derived growth factor (PDGF)- α which stimulates OPC proliferation while
247 preventing premature differentiation (Barateiro *et al.*, 2016). Conversely, insulin-like growth factor-1
248 (IGF-1), provided both by local synthesis in the brain and blood circulation (mainly from the liver),
249 promotes OL differentiation. In the PNS, large axons produce high amounts of Neuregulin-1 type III
250 which triggers SC differentiation towards a myelinating phenotype (Castelnovo *et al.*, 2017). Also,
251 several hormones are involved in myelin development and plasticity. In addition to hormones
252 produced by specialized endocrine glands, some hormones are produced locally in the nervous
253 system, as illustrated by IGF-1 but also several “neurosteroids” (Schumacher *et al.*, 2012). Moreover,
254 an increasing number of endogenous circulating compounds are now considered as hormonally
255 active, in particular when acting through nuclear receptors homologous to those of conventional
256 hormones. Here, it is important to mention the peroxisome proliferator-activated receptors (PPARs)
257 and their natural ligands (such as unsaturated fatty acids) which are notably involved in the
258 regulation of lipid metabolism (Maradonna and Carnevali, 2018; Mughal *et al.*, 2018).

259 Among the wide variety of human hormones, thyroid hormones are the most well-known extrinsic
260 signals regulating myelination. In humans, hypothyroidism is associated with hypomyelination and
261 intellectual disabilities (Mughal *et al.*, 2018). Indeed, triiodothyronine (T3) is necessary for normal
262 CNS myelination timing, and acts as a pro-myelinating factor *in vitro* and *in vivo* (Barateiro *et al.*,
263 2016). Moreover, thyroid hormones are involved in peripheral nerve myelination, with both OLs and
264 SCs expressing thyroid hormone receptors (TRs) (Barakat-Walter and Kraftsik, 2018). Among TRs,
265 TR β seems to play a role in transcription of genes associated with OL maturation, including *Mbp* (Lee
266 and Petratos, 2016). EDCs interfering with thyroid hormone signaling are thus prone to affect
267 myelination (Mughal *et al.*, 2018).

268 Besides thyroid hormones, myelin formation, degradation and repair can be modulated by many
269 other endocrine signals targeting myelinating cells directly or indirectly through neighboring cells
270 including neurons, astrocytes, and immune cells (Figure 1). Among these factors, the role of sex
271 hormones in myelin homeostasis is emphasized by sex-based differences observed in MS. This

272 pathology represents the most common cause of non-traumatic neurological disability in young
273 adults. Indeed, MS prevalence is much higher (about three times) in women than men, whereas men
274 tend to develop more severe clinical forms (Ysraelit and Correale, 2019). The CNS and PNS, which
275 receive steroids from the bloodstream and produce neurosteroids, express a wide variety of steroid
276 receptors (Jung-Testas and Baulieu, 1998; Kipp and Beyer, 2009). Several steroids have been shown
277 to act directly on myelinating cells. Indeed, progesterone shows pro-myelinating effects, notably by
278 increasing the expression of myelin proteins in differentiating SCs and OLs (Jung-Testas and Baulieu,
279 1998; Schumacher *et al.*, 2012). Similarly, 17 β -Estradiol stimulates SC and OL maturation (Jung-
280 Testas and Baulieu, 1998; Magnaghi *et al.*, 2004; Pansiot *et al.*, 2016), and estrogen receptors (ER α ,
281 ER β , G protein-coupled estrogen receptor/GPER/GPR30) are important for OPC differentiation
282 (Gonzalez *et al.*, 2016). In addition, both steroids have been shown to promote remyelination in
283 experimental models of demyelination (Chen *et al.*, 2016; Kumar *et al.*, 2013; Schumacher *et al.*,
284 2012). *In vivo*, neuroprotective impacts of progesterone and estradiol are actually based on multiple
285 modes of action including substantial immunomodulatory effects (Kipp and Beyer, 2009; Ysraelit
286 and Correale, 2019). For example, in animal models of MS (i.e. experimental autoimmune
287 encephalomyelitis/EAE and cuprizone-induced demyelination models), estrogens increase OL
288 differentiation and therefore remyelination, thus decreasing the severity of the disease. Using
289 targeted invalidation of ERs and selective pharmacological modulators, several molecular
290 mechanisms have been highlighted, including ER β -mediated effects directly in OLs as well as
291 immunomodulatory effects through ER α or ER β (Karim *et al.*, 2018; Khalaj *et al.*, 2013; L  lu *et al.*,
292 2011; Ohgomori and Jinno, 2019). In addition, after demyelination in the CNS, testosterone and
293 androgen receptor (AR) have been shown to favor astrocyte recruitment and OL-mediated myelin
294 regeneration (Bielecki *et al.*, 2016). Similarly, glucocorticoids exert pro-myelinating effects in SC-
295 neuron co-cultures and modulate myelination in the CNS, at least indirectly (Madalena and Lerch,
296 2017). Glucocorticoids are also well-known for their ability to exert anti-inflammatory effects, with
297 important implications in demyelinating conditions. To conclude this non-exhaustive presentation of
298 endocrine-mediated myelin regulations, recent studies have highlighted the role of PPAR signaling in
299 central and peripheral myelination, notably through regulation of lipid metabolism, as well as
300 neuroinflammation, demyelination and remyelination processes (Lin *et al.*, 2017; Montani *et al.*,
301 2018; Vall  e *et al.*, 2018).

302 To summarize, various hormonal receptors are expressed in the CNS and PNS which may constitute a
303 gateway for EDCs-mediated toxicity. EDCs can also exert indirect effects by disrupting the synthesis,
304 secretion and/or degradation of endogenous hormones implicated in myelin synthesis or
305 homeostasis (Figure 1).



307

308 **Figure 1. Possible levels of EDCs impacts on oligodendrocyte/Schwann cell differentiation and**
 309 **subsequent myelination**

310 Representations of oligodendrocyte (OL) and myelinating Schwann cell (SC) differentiation steps
 311 were adapted from (Fumagalli *et al.*, 2011; Schumacher *et al.*, 2012) and (Macklin and Rasband,
 312 2012), respectively. EDCs can interfere with myelination, demyelination and remyelination by many
 313 processes, including by disrupting hormone metabolism, by exerting direct effects on OL/SC
 314 differentiation processes, or by targeting indirectly neighboring neural cells as well as
 315 circulating/resident immune cells. CNPase: 2',3'-cyclic nucleotide 3'-phosphodiesterase, EDCs:
 316 endocrine disrupting chemicals, GFAP: glial fibrillary acidic protein, GPR17: G-protein-coupled
 317 receptor 17, MAG: myelin-associated glycoprotein, MBP: myelin basic protein, MOG: myelin
 318 oligodendrocyte glycoprotein, MPZ: myelin protein zero, NG2: Neural/glial antigen 2, OL:
 319 oligodendrocyte, OPC: oligodendrocyte precursor cell, PDGFR α : platelet-derived growth factor
 320 receptor alpha, PLP: proteolipid protein, PMP22: peripheral myelin protein 22, S100 β : S100 calcium
 321 binding protein β , SC: Schwann cell.

322

323 **3. Impacts of EDCs on myelin**

324 3.1. Persistent Organic Pollutants (POPs)

325 3.1.1. Polybrominated Diphenyl Ether (PBDE)

326 Polybrominated diphenyl ethers (PBDEs) are flame retardants added to furniture, electronic
327 enclosures, plastics, and circuitry. These substances accumulate in food chain and water and are
328 passed on through generations by crossing the placental barrier to the fetus and to the neonate
329 through lactation (Chen *et al.*, 2012b). These persistent organic pollutants (POPs) can disrupt thyroid
330 hormone signaling due to their structural similarities with thyroid hormones, with possible
331 deleterious consequences on neurodevelopment (Mughal *et al.*, 2018; Wang *et al.*, 2016). Indeed,
332 several epidemiological studies have linked early exposure to PBDE with various cognitive
333 impairments in children as well as disruption of thyroid hormone signaling, which was also
334 evidenced in diverse experimental models from fish to rodents (Mughal *et al.*, 2018).

335 Among the studies linking early exposure to PBDEs with neurodevelopmental issues in rodents, one
336 study specifically addressed their impacts on myelination (Fujimoto *et al.*, 2011). Early exposure to
337 decabromodiphenyl ether (DBDE) from gestational day (GD) 10 to postnatal day (PND) 20 induced
338 white matter hypoplasia in male rats from 100 ppm, measured by reduced corpus callosum area and
339 lower density of CNPase-positive OLs in the cingulum deep cortex. These defects were associated
340 with slight developmental hypothyroidism (Fujimoto *et al.*, 2011). In addition, the commercial PBDE
341 mixture DE-71 at 30 and 100 µg/L from 2 to 120 hours post-fertilization affected neural development
342 in zebrafish as evidenced by a decrease in the myelin-specific protein Mbp and in synapsin IIa
343 (Syn2a), a protein involved in synapse formation (Wang *et al.*, 2016). Additionally, these defects also
344 permanently altered spontaneous behavior, resulting in hypoactivity in zebrafish larvae. Similarly,
345 exposure to DE-71 (31.0, 68.7, and 227.6 µg/L) induced a decrease of *mbp* expression and had
346 different impacts on locomotor activity depending on the concentration (Chen *et al.*, 2012a). In
347 another study, parental exposure to DE-71 for 150 days at environmentally relevant doses (0.16, 0.8
348 and 4.0 µg/L), resulted in *mbp* and *syn2a* downregulation and diminished swimming speed in
349 zebrafish larvae. DE-71 was present in eggs, and elevated TH levels observed in exposed adults were
350 also found in their eggs (Chen *et al.*, 2012b). Thyroid hormone pathways are thus sensitive to PBDEs,
351 especially in the brain (Chen *et al.*, 2012b).

352 Furthermore, a direct impact of PBDEs on immature OLs was evidenced *in vitro* by investigating the
353 impacts of BDE-99 congener on human and murine neural progenitor cell (NPC) differentiation into

354 O4+ cells and their subsequent maturation (Dach *et al.*, 2017). Inhibition of differentiation into O4+
355 cells by BDE-99 was notably observed for human and mouse NPCs but was rescued by an antioxidant
356 (ascorbic acid) only in human cells. In addition, BDE-99 inhibited myelin-gene expression (*Mog*) in
357 mouse cultures but not in human cultures. This inhibition was not mediated by TRs because it was
358 still observed in NPCs derived from TR α and β knockout mice. While the data is limited, these results
359 suggest that molecular mechanisms linking PBDE exposure and disruption of myelination are
360 species-specific and involve mechanisms other than thyroid hormone signaling disruption, such as
361 oxidative stress.

362 3.1.2. Polychlorinated biphenyls (PCBs)

363 Polychlorinated biphenyls (PCBs) are synthetic environmental toxicants which were widely used
364 during the 20th century as insulators in electrical transformers and capacitors, in hydraulic and heat
365 transfer fluids, or as plasticizers and lubricants (Mughal *et al.*, 2018). Although banned since 3 or 4
366 decades in many countries, PCBs persist in the environment and can be found in water, soil and air
367 (Mughal *et al.*, 2018; Porterfield and Hendry, 1998). Humans are contaminated mostly by fish
368 consumption and pass it on to their progeny through placental transfer or lactation (Miller *et al.*,
369 2010; Porterfield and Hendry, 1998). PCBs are lipophilic and therefore accumulate in fat.
370 Accordingly, fish with lower fat content are less contaminated by these pollutants (Lüth *et al.*, 2018).
371 PCBs can therefore persist for several decades in the human organism, in which elimination half-lives
372 can reach 10 to 15 years for some congeners (Ritter *et al.*, 2011). PCBs can disrupt thyroid hormone
373 signaling and induce hypothyroxinemia (low T₄ levels) (Miller *et al.*, 2010; Mughal *et al.*, 2018; Zoeller
374 *et al.*, 2000). Clinical observations have correlated PCB levels in women to lower serum T₄ in the
375 neonates associated with altered neurological status and hypotonia (Quinete *et al.*, 2014). Indeed,
376 several TH-related neurological disorders have been associated with prenatal exposure to PCBs,
377 including intellectual and cognitive disabilities (Mughal *et al.*, 2018).

378 Since OL differentiation and myelination are tightly controlled by thyroid hormones,
379 neurodevelopmental consequences of PCB exposure are likely to involve disruption of myelination.
380 In this regard, experimental studies suggest that PCBs cause white matter changes associated with
381 altered behaviors. Aroclor 1254 (A1254), a mixture of 209 possible PCB congeners, caused
382 hypothyroxinemia in rat pups exposed from GD6 to PND21 (Zoeller *et al.*, 2000). *Mbp* expression
383 was downregulated possibly as a result of hypothyroxinemia for the lower dose of 1 mg/kg. At
384 higher doses, *Mbp* and RC3/Neurogranin (*Nrgn*) genes, which are thyroid-responsive, were regulated
385 in a thyro-mimetic stimulating manner at PND15, but not at PND5 or PND30, possibly resulting from
386 high PCB concentrations in the brain at this stage. This contradictory result suggests that PCBs were

387 not solely acting by inducing hypothyroxinemia. This hypothesis was further reinforced by showing
388 that A1254 exposure at 5 mg/kg from GD7 to PND15 did not fully reproduce the effects of
389 hypothyroidism in the white matter (Sharlin *et al.*, 2006). In fact, A1254 decreased both the number
390 of OLs and astrocytes while hypothyroidism decreased the number of OLs and increased astrocyte
391 density. These studies thus illustrate the complexity of PCB effects on brain development which
392 could also be linked to the chemical diversity of PCB congeners (Sharlin *et al.*, 2006; Zoeller *et al.*,
393 2000). This complexity was further highlighted in a study implicating interleukin (IL) 6 in the impact
394 of PCBs on cerebellar myelination in a sex specific manner (Miller *et al.*, 2010). Indeed, early
395 exposure of rats to PCBs during the same period (GD6 to weaning) induced hypothyroxinemia in
396 males and females throughout postnatal development. However, at PND21, PCBs increased MBP
397 and decreased GFAP levels in males but had opposite effects in females. Elevated levels of IL-6 were
398 concomitantly observed in males only, suggesting a role for IL-6 in the impact of PCBs on cerebellar
399 myelination and associated motor functions, specifically in males. In females, the opposite effects of
400 PCBs may be explained by the estrogeno- and thyro-mimetic effects of OH-PCBs metabolites,
401 particularly by disrupting TR β 1 signaling since its activation is important for *Mbp* transcription (Miller
402 *et al.*, 2010). At first, PCBs would induce hypothyroxinemia (Zoeller *et al.*, 2000). Thyroid hormone
403 deficiency may then cause a decrease in the number of OLs and an increase of astrocyte density
404 (Sharlin *et al.*, 2006). PCB congeners may exert agonistic or antagonistic effects on thyroid hormone
405 signaling which may be dose, species, and congener dependent. Indeed, PCBs interact with TRs,
406 thyroid hormone binding proteins and transport systems (Porterfield and Hendry, 1998; Zoeller *et al.*
407 *et al.*, 2000). PCBs can also affect calcium signaling and induce reactive oxygen signaling, both of which
408 can disrupt OL differentiation but have not been studied in this context (Sharlin *et al.*, 2006).

409 3.1.3. 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD)

410 Dioxins, which include polychlorinated dibenzo-dioxins (PCDDs), polychlorinated dibenzofurans and
411 dioxin-like PCBs, are persistent environmental pollutants generated by burning of domestic or
412 industrial waste or by herbicide production (Fernández-González *et al.*, 2015). TCDD, which belongs
413 to PCDD group, is considered as the most toxic dioxin. As other POPs, dioxins contaminate humans
414 by food of animal origin, accumulate in fat tissues and expose fetuses and babies by crossing the
415 placental barrier and passing into the milk. Epidemiological evidence has linked exposure to various
416 dioxins with neurological disabilities especially when occurring during CNS development, including
417 motor and cognitive deficits (Fernández-González *et al.*, 2015). Neurodevelopmental toxicity of
418 dioxins has notably been evidenced in children, mostly boys, exposed to dioxins *in utero*, after
419 environmental contamination by Agent Orange in Vietnam and after Seveso industrial accident in
420 Italy (Ames *et al.*, 2019; Pham *et al.*, 2019). Dioxins are well-characterized EDCs which target

421 multiple signaling systems, and in particular thyroid hormone signaling, as many other POPs. TCDD
422 also interferes with estrogen, progesterone and androgen receptor pathways and is a potent agonist
423 of the dioxin/aryl hydrocarbon receptor (AhR) (Fernández *et al.*, 2010). In addition to disrupting
424 hormonal signaling involved in myelin formation and homeostasis, TCDD may thus also exert its
425 toxicity through AhR, whose roles in myelination and myelin integrity have been recently highlighted
426 (Juricek *et al.*, 2017; Shackleford *et al.*, 2018).

427 TCDD toxicity on myelination has been evidenced experimentally in male rats, in which a single dose
428 TCDD at GD18 provoked an alteration of myelination timing in neonatal rats while being mildly toxic
429 to the mother (Fernández *et al.*, 2010). The myelination was delayed in several brain regions, as
430 indicated by the persistence of OPC markers such as *Olig1* and *Pdfgra* genes until adulthood, and the
431 delayed expression of myelin markers such as CNPase and MBP. TCDD *in utero* exposure therefore
432 caused lasting consequences on myelin. In addition, *ex vivo* experiments performed by collecting the
433 subventricular zone (SVZ) of adult dams indicated that TCDD exposure had altered the potential of
434 stem cells and NSCs to generate OLs, which could therefore affect remyelination potential
435 (Fernández *et al.*, 2010). Although the authors did not investigate the mechanisms of TCDD toxicity
436 on OLs and myelination, they speculated that TCDD operated through thyroid hormone disruption.

437 In adults, TCDD induced demyelination in the hippocampus of female rats 3 weeks after
438 intramuscular administration, which was associated with inflammatory reaction and decrease of ER α
439 expression (Rosińczuk *et al.*, 2015). In an experimental autoimmune encephalomyelitis (EAE) mouse
440 model induced by MOG injection, subchronic low dose of TCDD was found to inhibit the immune
441 response mediated by interferon- γ (IFN- γ) or IL-17 producing CD4⁺ cells (TH1 or TH17 cells) and to
442 increase regulatory T (Treg) cells (Yang *et al.*, 2016). Due to the important roles of AhR in immune
443 homeostasis, the authors hypothesized that AhR activation was involved in the TCDD-mediated
444 immunomodulation in this model.

445 3.2. Non-Halogenated Phenolic Chemicals

446 3.2.1. Bisphenol A

447 Bisphenol A (BPA) is a widespread synthetic xenoestrogen mainly used in the production of
448 polycarbonate plastics and epoxy resins. BPA is the EDC for which health effects have been the most
449 extensively studied. Its suspected deleterious impacts on health in humans, strongly supported by
450 experimental evidence, have driven regulatory decisions restricting BPA use in consumer products.
451 In humans, neurodevelopmental toxicity is suggested by epidemiological data linking BPA exposure
452 during pregnancy and/or postnatal development with later neurodevelopmental disorders such as
453 attention deficit hyperactivity disorder (ADHD) (Rochester *et al.*, 2018). BPA crosses the placental

454 barrier, is secreted in milk and crosses the BBB, supporting direct effects of BPA in the CNS (Negri-
455 Cesi, 2015; Nesan *et al.*, 2018). The role of BPA in neurodevelopmental disorders is credited by
456 experimental studies linking BPA exposure during gestation, lactation or late postnatal development
457 with lasting behavioral deficits in rodents (Nesan *et al.*, 2018; Rochester *et al.*, 2018; Tandon *et al.*,
458 2020; Tiwari *et al.*, 2015; Xu *et al.*, 2017). At the molecular level, BPA mainly exerts estrogeno-
459 mimetic effects but also several other endocrine disrupting mechanisms, in particular anti-
460 androgenic and anti-thyroid effects (Nesan *et al.*, 2018).

461 Regarding cellular targets of BPA in the nervous system, only a few studies have reported specific
462 effects on OLs and myelination to this date. Initial evidence was presented by an *in vitro* study in
463 which BPA inhibited the differentiation of primary mouse OPCs, as evidenced by a blockade of MBP
464 up-regulation, by interfering with TH signaling mostly by decreasing the expression of TR β 1 (Seiwa *et al.*,
465 2004). The negative impact of BPA on OPC differentiation was later confirmed in primary OPCs
466 derived from rat hippocampal NSCs (Tiwari *et al.*, 2015). In addition to decreasing their myelinating
467 potential, BPA affected OPC proliferation, as evidenced by analyzing the number and size of
468 oligospheres (which are firstly grown from NSCs) as well as via bromodeoxyuridine (BrDU)
469 incorporation, which reflects proliferation in dissociated OPC cultures. It is noteworthy that at the
470 lowest concentration tested (1 μ M), BPA increased proliferation, and that this effect was reversed
471 for higher concentrations. This non-monotonic dose-response illustrates a typical characteristic of
472 EDCs.

473 *In vivo*, early BPA exposure caused a reduction in myelin-specific protein expression including MBP,
474 PLP and MAG, and in monocarboxylate transporter (MCT) 1 in the rat hippocampus (Tiwari *et al.*,
475 2015; Xu *et al.*, 2017). At the ultrastructural level, BPA exposure during gestation and lactation (40
476 μ g/kg/day, G6 to PND21) or late postnatal development (PND21 to PND90) disrupted the
477 myelination process in the rat hippocampus, causing a reduction in axon caliber, altered *g-ratio* and
478 myelin decompaction associated with a decrease in cognitive function in offspring (Tiwari *et al.*,
479 2015). Moreover, BPA exposure of male rats through drinking water of lactating mothers (0.1 mg/L,
480 PND0 to PND21) induced persistent myelination defects in the hippocampus including OL loss and
481 reduction in the number of myelinated axons without alteration of the *g-ratio*, correlated with a
482 deficit of contextual fear memory (Xu *et al.*, 2017). Intriguingly, paternal BPA diet (before
483 conception) induced a decrease in the expression of MBP protein and several myelin-specific genes
484 in the prefrontal cortex of male offspring. This decreased expression was associated with altered
485 social behaviors, reduced exploration activity and increased anxiety (Luo *et al.*, 2017). Proteomic
486 analysis suggested that myelin alterations may be mediated by increased endoplasmic reticulum

487 stress (Luo *et al.*, 2017). These intergenerational impacts of BPA on CNS myelination could be
488 mediated by epigenetic mechanisms.

489 In addition to mentioned effects of BPA on TR β expression, few other studies have investigated the
490 molecular mechanisms by which BPA might directly alter OL differentiation and subsequent
491 myelination (Seiwa *et al.*, 2004). In particular, BPA exposure through lactation caused OL loss in the
492 hippocampus by disrupting ER signaling (Xu *et al.*, 2017). During late postnatal development, BPA
493 was shown to cause myelination abnormalities by inhibiting Notch canonical pathway, which is
494 essential for the formation and maintenance of OPCs while inhibiting OL differentiation (Tandon *et al.*
495 *et al.*, 2020). BPA inhibited OPC proliferation *in vitro* with a decreased size and number of oligospheres
496 and further caused a decline in OPC differentiation. BPA also increased cleaved caspase 3 levels,
497 inducing apoptosis in the hippocampus. Curcumin, which up-regulated the Notch pathway,
498 mitigated BPA effects both *in vitro* and *in vivo*. These effects notably impacted OL proliferation and
499 differentiation, myelination in hippocampus and associated behavioral deficits (Tandon *et al.*, 2020).
500 In summary, many questions remain concerning the molecular mechanisms of BPA-mediated
501 neurotoxicity towards OLs, in particular regarding possible interactions between ER signaling and
502 Notch pathway and involvement of other hormonal receptors. The mechanisms underlying
503 permanent effects in adults after early BPA exposure strongly suggest a role of epigenetic
504 mechanisms through ER activation (Xu *et al.*, 2017).

505 BPA has been implicated in demyelination in several mouse models. In a model of MS based on
506 virus-induced demyelination, perinatal BPA exposure increased inflammation and accelerated the
507 symptom onset (Brinkmeyer-Langford *et al.*, 2014). According to a recent study, BPA alone may
508 induce demyelination, as evidenced in adult male mice exposed to BPA during a 60 day period (40 or
509 400 $\mu\text{g}/\text{kg}/\text{day}$) (Khan *et al.*, 2019). Chronic BPA exposure resulted in a decrease of mRNA levels of
510 *Mbp*, *Mag* and *Cnp*. Chronic exposure also resulted in the downregulation of genes coding for nestin,
511 involved in growth and survival of neural and oligodendroglial progenitors, and neural cell adhesion
512 molecule (NCAM), a marker of neurotoxicity in diseases such as MS and Alzheimer disease. These
513 deficits were associated with an increase in mechanical allodynia, an impairment in spatial memory
514 and a decrease in muscle coordination (Khan *et al.*, 2019). In this context, BPA toxicity was attributed
515 to increased neuroinflammation and oxidative stress. Indeed, BPA increased the expression levels of
516 several cytokines involved in axonal and myelin degeneration. These cytokines include IL-17, IL-1 β ,
517 IL-12p40, IL-10 and tumor necrosis factor (TNF)- α . Additionally, increased protein carbonylation, a
518 marker of oxidative stress, was evidenced (Khan *et al.*, 2019). BPA can also bind to human serum
519 albumin (HSA), causing autoimmunization (Datis Kharrazian and Vojdani, 2017). Importantly, the
520 levels of BPA-HSA in healthy human subjects have been correlated with those of antibodies against

521 MBP and MOG, which are key biomarkers of MS. This suggests that BPA-HSA triggers the production
522 of autoantibodies against myelin proteins. However, further studies are required to specifically link
523 BPA exposure to autoimmune demyelination (D. Kharrazian and Vojdani, 2017).

524 3.2.2. Bisphenol A diglycidyl ether (BADGE)

525 BADGE is a **derivate of BPA** found in the inner coating of canned beverages (Miyazaki *et al.*, 2020). It
526 is also an EDC which has been reported to bind, similarly to BPA, to TR β 1 (Zhang *et al.*, 2016).
527 **Besides, BADGE is a well-established PPAR γ antagonist, but could also act as an agonist depending**
528 **on the cellular context (Bishop-Bailey *et al.*, 2000; Wright *et al.*, 2000).** Although BPA effects on
529 brain development and behavior have been studied for more than a decade, those of BADGE have
530 only been of interest recently (Miyazaki *et al.*, 2020; Seiwa *et al.*, 2004). **Regarding specific effects of**
531 **BADGE on myelin,** two studies reported **an** exacerbation of demyelinating condition in an EAE mouse
532 model (Raikwar *et al.*, 2006, 2005). In this context, **BADGE increased T cell proliferation and Th1**
533 **differentiation (Raikwar *et al.*, 2005).** **Used as a PPAR γ antagonist, BADGE reversed the protective**
534 **effects of PPAR γ agonists on EAE (Raikwar *et al.*, 2006).** **Additional studies are needed to better**
535 **understand the potential impacts of BADGE on myelin. In this regard, several BPA analogues such as**
536 **bisphenol S and F, which are increasingly used to replace BPA, also require the attention of**
537 **researchers.**

538 3.3. Halogenated Phenolic Chemicals (HPCs): Triclosan

539 Triclosan (5-chloro-2-(2,4-dichlorophenoxy) phenol) is an anti-bacterial agent used in many
540 consumer products such as personal care products, shoes and household products (Pullaguri *et al.*,
541 2020). Several studies reported thyroid disrupting effects of triclosan, which prompted the study of
542 its toxic effects on neurodevelopment (Jackson-Browne *et al.*, 2020). Although some epidemiological
543 studies showed no association between triclosan exposure and thyroid hormone disruption during
544 pregnancy in women, others showed an inverse association between maternal and childhood
545 urinary triclosan and IQ scores, behavioral outcomes at 8 years old and academic achievements
546 (Derakhshan *et al.*, 2019; Jackson-Browne *et al.*, 2020). To gain insight into specific effects of
547 triclosan on myelination, a recent study investigated the effect of triclosan exposure (0, 62.5, 125,
548 250 μ g/L) on zebrafish larvae (Ling *et al.*, 2020). Triclosan inhibited OPC differentiation by down-
549 regulating miR-219 expression, which participates in silencing myelination inhibitors. The decrease in
550 expression of miR-219 therefore led to a rapid increase in the proliferation of OPCs and a decrease
551 of myelin marker genes. The authors also demonstrated that miR-219 down-regulation involved DNA
552 methylation, thus highlighting that triclosan toxicity was mediated by a sequence of epigenetic
553 modifications in OPCs (Ling *et al.*, 2020). Importantly, miR-219 is an evolutionarily conserved miRNA

554 whose function in OL maturation had previously been evidenced in mice, thus reaffirming the
555 significance of this breakthrough in understanding triclosan toxicity on myelin (Zhao *et al.*, 2010).

556 3.4. Heavy metals

557 Heavy metals are natural elements with relatively high density and atomic mass, most of which are
558 toxic even at low concentrations. Lead, cadmium, arsenic and mercury are the pertinent heavy
559 metals that have been identified as myelin toxicants. Because their multiple toxicity mechanisms
560 include endocrine disruption, we review here the current knowledge on toxicity of these heavy
561 metals towards myelin and the molecular mechanisms elucidated so far. It is noteworthy that
562 gender differences in the neurotoxicity of metallic elements, which are proven for some compounds
563 although still insufficiently studied, argue in favor of an interaction between heavy metals and the
564 endocrine system (Llop *et al.*, 2013).

565 3.4.1. Lead

566 Lead (Pb²⁺) exposure is mainly achieved through gasoline combustion, while children are mostly
567 exposed through ingestion of leaded paint residues found in dust and soil. Children can also be
568 exposed to lead through toys and art materials (Brubaker *et al.*, 2010). Several guidelines and
569 regulations were adopted to reduce lead exposure. For example, in the U.S., reduction of lead in
570 drinking water act (RLDWA) prohibited the use of lead pipes in 2011. Lead was banned in consumer
571 paints in 1978 and gradually phased out in gasoline (Pohl *et al.*, 2017). Lead is an endocrine disruptor
572 as it disturbs hormone signaling both in females and males. In female rats, lead was shown to reduce
573 the number of uterine ERs, delay puberty, reduce plasma estrogen levels and alter their synthesis.
574 These disturbances may be explained by an impact of lead on the hypothalamus-pituitary axis, and
575 notably on luteinizing hormone release. Lead also decreased plasma testosterone in male rats and
576 delayed pubertal growth by delaying that of the GH hormone system (Iavicoli *et al.*, 2009).

577 Lead poisoning, also called “saturnism”, is particularly detrimental for children and seems to affect
578 more severely boys than girls (Llop *et al.*, 2013). Severe lead poisoning, generally by chronic
579 exposure, can cause encephalopathy and death, or, in less severe cases, permanent neurological
580 disorders. Lead diffuses and accumulates in the brain, where it notably causes hypomyelination and
581 demyelination (Deng and Poretz, 2001a; Maiuolo *et al.*, 2019). Epidemiological evidence associates
582 developmental lead exposure with a reduction of gray matter and alterations in myelin structure in
583 the white matter. These abnormalities were linked to a reduction in cognitive function, altered
584 behavior and ADHD (Cecil *et al.*, 2011; Jones *et al.*, 2008; Sánchez-Martín *et al.*, 2013). *In vivo*, lead
585 exposure during gestation slightly inhibited myelinated axon fibers formation in the cerebellum of

586 rat offspring, particularly in Purkinje cells. This developmental toxicity was characterized by lower
587 expression of OL and myelination markers, such as MBP and MAG, and was associated with
588 increased glutamatergic, oxidative (nuclear factor erythroid-2-related factor 2/NRF2 and
589 manganese-dependent superoxide dismutase/Mn-SOD), and inflammatory (IL-1 β and TNF- α)
590 stresses (Nam *et al.*, 2020, 2019a, 2019b, 2019c). Lead exposure during lactation also increased *Plp1*
591 and *Mbp* mRNA expressions in the frontal cortex of rat offspring at weaning, suggestive of an earlier
592 expression onset of these genes and a disturbance in normal OL differentiation time-course (Zawia
593 and Harry, 1996). Lead exposure during gestation also caused a decrease in myelin galactolipids
594 through downregulation of enzymes involved in their biosynthesis such as UDP-galactose:ceramide
595 galactosyltransferase (CGaIT/UGT8A), whose mRNA expression marks the onset of OPC
596 differentiation. Additionally, 3'-phosphoadenosine-5'-phosphosulfate: cerebroside sulfotransferase
597 (GalCST/GAL3ST1), necessary for sulfatide synthesis, was downregulated (Deng and Poretz, 2001a).
598 The authors observed similar effects *in vitro* by exposing rat OLs with 1 μ M lead 24h before and 48h
599 during differentiation, indicating a direct toxicity of this metal on oligodendroglial differentiation
600 (Deng and Poretz, 2001b). *In vitro*, lead also interfered with the differentiation of the CG-4 OPC-like
601 cell line whereas mature OLs seemed to be less sensitive to lead toxicity (Deng *et al.*, 2001). This
602 suggests that OPCs, and not mature OLs, are the primary targets of lead *in vivo*. They also
603 demonstrated that lead toxicity on OL differentiation involves the activation of protein kinase C
604 (PKC) (Deng and Poretz, 2003). To conclude on myelination, a study also showed negative effects of
605 lead during a late neurodevelopmental stage (extending from puberty to adulthood), as revealed by
606 a decrease in MBP staining in the rat cerebellum (Leão *et al.*, 2020).

607 While developmental lead exposure causes hypomyelination, lead poisoning progressively causes
608 brain demyelination (Morelli *et al.*, 2012). Acute lead intoxication in rat altered myelin morphology
609 as it loosened the myelin sheaths and caused the appearance of ovoid-shaped swollen fragments
610 (Dabrowska-Bouta *et al.*, 2000). Chronic lead intoxication in rats at environmental doses also caused
611 a reduction in myelination and myelin integrity, altered BBB permeability and OL morphology
612 (Dabrowska-Bouta *et al.*, 2004, 1999). It also induced a drop in myelin glycoprotein levels such as
613 MAG and MOG and in SH levels in proteins (Dabrowska-Bouta *et al.*, 2008, 1999). In addition,
614 phosphatidylethanolamine (PE) levels increased along with the ratio of PE: phosphatidylcholine (PC).
615 These alterations in phospholipid composition and their distribution in the membrane could account
616 for altered fluidity of the membrane, especially since myelin is mainly composed of lipids
617 (Dabrowska-Bouta *et al.*, 1999). CNPase enzyme activity was decreased in acute and chronic models
618 of intoxication (Dabrowska-Bouta *et al.*, 2004, 2000). Interestingly, lead interferes with heme
619 biosynthesis in OLs and accumulates in myelin sheath, thus modifying its structure. This effect has

620 been demonstrated in cultures of mouse dorsal root ganglia (DRG) and in brains of chronically
621 poisoned rats (Morelli *et al.*, 2012). Lead poisoning could therefore be an environmental trigger of
622 MS (Morelli *et al.*, 2012). In these contexts, it is noteworthy to discuss mechanism that lead might
623 employ, such as thiol-complexing action, which causes toxicity through enzymatic inhibition,
624 especially relevant in pathways associated with heme synthesis.

625

626 3.4.2. Mercury

627 Mercury (Hg) is a ubiquitous element in the environment (Yang *et al.*, 2020). Elemental, inorganic,
628 and organic forms of Hg coexist and are all toxic for human health, especially towards the nervous,
629 urinary, and immune systems. Elemental Hg (Hg^0) is mainly responsible for intoxications of artisanal
630 gold miners which use Hg in gold extraction processes. After contamination by inhalation, Hg^0
631 crosses the BBB and is oxidized within the brain to inorganic Hg^{2+} which accumulates and causes
632 neurological symptoms including tremors and ataxia. The general population is, to a lesser extent,
633 also exposed to Hg^0 by dental amalgam fillings (Yang *et al.*, 2020). However, the main source of non-
634 occupational Hg exposure is food, especially fish consumption. Methylmercury (MeHg) is particularly
635 concerning primarily due to its comparatively high bioavailability via oral routes and its subsequent
636 accumulation in the CNS (Yang *et al.*, 2020). MeHg is a toxic organometal with a short alkyl chain
637 (Philbert *et al.*, 2000). Upon reaching the brain, MeHg is demethylated into Hg^{2+} , which persists and
638 accumulates during the person's lifetime (Philbert *et al.*, 2000). Whatever the primarily form of Hg
639 contamination, Hg^{2+} is primarily responsible for Hg toxicity in the nervous system. The first massive
640 cases of methylmercury poisoning were reported in the 1950s around the Japanese Minamata Bay
641 and were known as "Minamata Disease" (Takeuchi *et al.*, 1959). MeHg-induced neurological
642 disabilities included peripheral sensory neuropathy, tremor and ataxia (Eto *et al.*, 2010; Philbert *et*
643 *al.*, 2000; Takeuchi *et al.*, 1959). Biopsies and autopsies revealed that MeHg was responsible for
644 lesions mainly localized in specific areas of the cerebral cortex, in the cerebellum and in peripheral
645 nerves (Eto *et al.*, 2010). *In utero* exposure induced even more severe disabilities similar to cerebral
646 palsy and referred to as fetal (or congenital) Minamata disease (Eto *et al.*, 1992). Studying the
647 consequences of this massive poisoning case surfaced crucial information on Hg neurotoxicity.
648 However, the current knowledge on myelin toxicity of Hg is mainly reliant on experimental studies.

649 *In vivo*, early exposure to MeHg disrupted MBP, CNP and PLP expressions in the cerebellum of rat
650 pups, mostly at the transcriptional level, and reduced OL cell population (Grundt and Neskovic, 1985;
651 Padhi *et al.*, 2015; Padhi and Pelletier, 2012). *In vitro*, MeHg induced degeneration of axons and
652 myelin in cultures of newborn mouse cerebellum (Kim, 1971). Several studies suggested that Hg-
653 mediated myelin toxicity during development may involve disruptions of myelin lipid metabolism.

654 Indeed, early postnatal MeHg exposure reduced the activity of brain CGaIT/UGT8A which is
655 responsible for the synthesis of essential galactolipids in the myelin sheath (Grundt and Neskovic,
656 1985). *In vitro*, Hg²⁺ also inhibited fatty acid (FA) elongation in mouse microsomal preparations,
657 depleting very long chain FAs found in myelin possibly through alteration of sulfhydryl groups
658 (Bourre and Dumont, 1985). MeHg was also reported to induce a decrease of α -hydroxy FAs to non-
659 substituted FAs ratio in myelin cerebroside of suckling rats (Grundt *et al.*, 1980). Furthermore, a
660 recent study showed a dysmyelinating effect of *in utero* chronic exposure to MeHg in the rat
661 hippocampus, as evidenced by decreased MBP levels at PND30 (Heimfarth *et al.*, 2018). Structural
662 defects were associated with increased anxiety-like behavior, decreased exploration behavior, as
663 well as long and short term memory deficits (Heimfarth *et al.*, 2018). In this context, GFAP was
664 overexpressed, which pointed towards increased astrocyte reactivity (Heimfarth *et al.*, 2018).

665 Besides developmental exposure, Hg is also suspected to contribute to demyelination in adulthood.
666 A recent study established that long term exposure of adult rats to low doses of MeHg altered the
667 hippocampal proteome, notably through reduced expression of MOG and MAG and increased
668 expression of GFAP, along with altered spatial and social memories (Bittencourt *et al.*, 2019). Hg is
669 also suspected to increase MS exacerbations in subjects with silver dental fillings (amalgams)
670 (Siblerud and Kienholz, 1994). *In vitro*, HgCl₂ was cytotoxic for the human oligodendroglial cell line
671 MO3.13 in which apoptosis was observed after 24 hours at 25 μ M (Issa *et al.*, 2003). This suggests
672 that Hg may have a direct impact on OL survival, although the concentration used was much higher
673 (by 500-fold) than blood mercury concentration in individuals with amalgams. In an EAE mouse
674 model of MS induced by MOG, Hg accelerated disease progression through oxidative stress along
675 with apoptosis and mitochondrial toxicity, supporting an aggravating role of Hg in MS progression
676 (Kahrizi *et al.*, 2016). In another study, HgCl₂ at low doses independently damaged the central myelin
677 sheath in the spinal cord of adult rats after long term exposure (Corrêa *et al.*, 2020). In this model,
678 HgCl₂ provoked ultrastructural changes in the myelin sheath including a loss of compaction and
679 altered levels of myelin structural proteins, as revealed by proteomic profiling (Corrêa *et al.*, 2020).
680 In addition, oxidative and nitrosative stresses were observed. The demyelinating impacts of Hg may
681 also involve immunomodulatory mechanisms, as suggested by the induction of anti-neural
682 autoantibodies in rats after MeHg exposure, including anti-MBP IgGs (H. A. el-Fawal *et al.*, 1996).
683 Several studies also correlated the levels of anti-neural autoantibodies (including anti-MBP and anti-
684 MAG) with Hg exposure in children diagnosed with autism (Kern *et al.*, 2020).

685 In Minamata disease patients, the most obvious impacts of MeHg on myelin were observed in the
686 PNS. Indeed, chronic exposure to MeHg caused a peripheral sensory neuropathy (Eto *et al.*, 2010,
687 1992; Takeuchi *et al.*, 1978, 1959). Biopsies of adult sensory nerves such as sural nerves showed

688 severe demyelination associated with SC proliferation (Eto *et al.*, 2010). In fetal cases of Minamata
689 disease, biopsies also revealed a decreased number of myelinated peripheral nerve fibers in the
690 sural nerves, in which myelin sheaths were abnormal and distended, but SC proliferation was not as
691 important compared to adult cases (Takeuchi *et al.*, 1978). In agreement with this data, MeHg
692 intoxication in rats caused swelling and loosening of myelin sheaths in the dorsal root ganglia,
693 supporting Hg toxicity for peripheral myelin (Schjønning *et al.*, 1998).

694 Similarly to other metals, Hg toxicity is mainly mediated by thiol binding, generation of oxidative
695 stress and disruption of calcium homeostasis (Yang *et al.*, 2020). These mechanisms are possibly
696 involved in endocrine disruption, notably by blocking the activities of enzymes involved in hormone
697 synthesis. Hg is also suspected to exert many other effects, especially at chronic exposition levels,
698 including on the reproductive system as observed in several wild animal species (Yang *et al.*, 2020). It
699 is not known yet if endocrine-related mechanisms are involved in Hg impacts on myelin.

700 3.4.3. Cadmium

701 Cadmium (Cd) is a trace element that accumulates in an organism due to its low rate of excretion
702 (Wang and Du, 2013). Aside from workers exposed to Cd-containing fumes especially during welding
703 work, the general population is mainly exposed to cadmium through cigarette smoke and ingestion
704 of contaminated food (Hossain *et al.*, 2009). While the brain is a primary target for lead and organic
705 mercury, Cd is mainly toxic for the lungs, kidneys and bones. Regarding the subject of this review, Cd
706 also exerts neurotoxic effects and has notably been associated with several neurodevelopmental
707 deficits, neurodegenerative diseases and peripheral neuropathies (Wang and Du, 2013). In addition
708 to direct cytotoxicity involving oxidative stress, thiol binding and competition with essential cations,
709 Cd interferes with calcium homeostasis by altering the metabolism and function of calciotropic
710 hormones (Schutte *et al.*, 2008). Cd poisoning negatively affects thyroid hormone levels and may
711 also affect the expression of steroid hormone receptors in the brain following early exposure
712 (Ishitobi *et al.*, 2007). Furthermore, *in vitro* and *in vivo* studies demonstrated that Cd, as well as
713 other metals termed metalloestrogens, could bind to ERs and induce agonist responses (Darbre,
714 2006; Skalny *et al.*, 2018). These endocrine-related mechanisms may thus participate in Cd
715 neurotoxicity and damage to myelin.

716 In the mature CNS, the BBB constitutes a relative protection against direct central neurotoxicity of
717 Cd. However, this barrier is not fully efficient during development, and Cd has further been shown to
718 disrupt BBB permeability (Wang and Du, 2013). This point, coupled with the fact that brain
719 development is associated with a critical window of vulnerability, may explain why adult rats are less
720 sensitive to Cd neurotoxicity in comparison to newborn rats, especially as myelination has increased

721 (Gabbiani *et al.*, 1967). There is only sparse evidence for Cd toxicity on myelin, and most studies link
722 Cd exposure to secondary myelin injury rather than disruption of myelin formation. In isolated rat
723 optic nerve preparations, Cd²⁺ caused axonal swelling accompanied by large empty spaces beneath
724 myelin sheaths through the disruption of mitochondrial respiration (Fern *et al.*, 1996). In agreement
725 with this *in vitro* observation, small size myelinated axons of rat optic nerves displayed a destruction
726 of their myelin sheath after *in vivo* Cd exposure. This destruction, which also relied on disruption of
727 mitochondrial respiration, was even more significant in diabetic rats, with diabetes being a source of
728 neuropathy by itself (Demir *et al.*, 2003). In adult zebrafish, cadmium chloride (CdCl₂) altered myelin
729 structure in the CNS as revealed by an up-regulation in *mpz* mRNA levels (which, in zebrafish, is
730 expressed in central myelin), while other myelin structural genes remained unaltered (*mbp*, *plp1*)
731 (Monaco *et al.*, 2016). *In vivo*, post-natal Cd exposure altered brain lipid composition in weanling
732 rats, as revealed by a decrease in general lipid concentration including characteristic lipids of myelin
733 (cerebrosides, sulfatides, non-esterified cholesterol and ethanolamine plasmalogens) (Gulati *et al.*,
734 1986). These lipid alterations in the brain suggest hypomyelination. In the rat PNS, Cd poisoning
735 induced a peripheral polyneuropathy that involved demyelination, beginning at the node of Ranvier,
736 and a disruption of the remyelination process (Sato *et al.*, 1978). As shown for optic nerves in the
737 CNS, Cd also enhanced diabetic-induced damage in rat peripheral myelin (Demir *et al.*, 2002).

738 The mechanisms involved in Cd toxicity on myelin may include direct impacts on myelinating cells.
739 Indeed, in isolated OLs, Cd accumulated in OPCs and induced cell death through reactive oxygen
740 species (ROS) production, reduction in glutathione levels and mitochondrial-dependent apoptosis,
741 whereas differentiated OLs were less vulnerable to Cd (Almazan *et al.*, 2000; Hossain *et al.*, 2009).
742 More recently, Cd concentration in serum was found to be a positive predictor of anti-MBP
743 antibodies levels in children with diagnosed autism spectrum disorder, suggesting that autoimmune
744 mechanisms may contribute to myelin toxicity of Cd during development (Skalny *et al.*, 2018). The
745 involvement of endocrine-related mechanisms in Cd-induced myelin toxicity has not been
746 demonstrated profoundly in previous research findings and therefore merits further investigation.

747 3.4.4. Arsenic

748 Arsenic (As) is a ubiquitous metalloid used in the production of pesticides, pigments, alloys and
749 antifouling paint that poison humans through contaminated water (Srivastava *et al.*, 2014). Arsenic
750 has three oxidation states : elemental (0), trivalent (-3, +3 or As-III) and finally pentavalent (+5 or As-
751 V) (Rodríguez *et al.*, 2003). In the human liver, arsenate reductase catalyzes the reduction of
752 arsenate (As-V, AsO₄³⁻) to arsenite (As-III, AsO₃³⁻), which can interact with thiols (Rodríguez *et al.*,
753 2003). In ancient Middle Age and Renaissance times, arsenical compounds were used as poison. As is

754 also present in ancient Chinese medicine, realgar, and As-III is used in chemotherapy (Zhang *et al.*,
755 2020). Environmental As released by industry sediments in water and can therefore be found in fish,
756 resulting in human exposure through food contamination. Occupational exposure occurs mainly
757 through inhalation during mining activities and has been linked to several types of cancers including
758 lung cancer. It is also linked to blackfoot disease, a peripheral vascular disorder resulting in gangrene
759 of lower extremities (Rodríguez *et al.*, 2003). Among these multiple adverse health effects, As
760 neurotoxicity has been described mainly in sensory fibers of peripheral nerves and involves
761 nonspecific mechanisms including thiol binding, mitochondrial dysfunction, oxidative stress and
762 apoptosis (Mochizuki, 2019; Rodríguez *et al.*, 2003). Arsenite blocks sulfhydryl groups in proteins and
763 enzymes, such as enzymes and cofactors involved in carbohydrate metabolism (Cavanagh, 1973;
764 Rodríguez *et al.*, 2003). Also, As has proven to disrupt glucocorticoid, mineralocorticoid,
765 progesterone and androgen receptors-mediated gene regulations in a non-monotonic dose-
766 response manner (Davey *et al.*, 2007). Indeed, lower doses of As enhanced gene transcription
767 whereas higher doses had suppressing effects. In addition, As inhibited ER-dependent gene
768 transcription both *in vitro* and *in vivo* (Davey *et al.*, 2007). Hormone disrupting effects of As could
769 thus be involved in its neurotoxicity.

770 Several epidemiological studies showed that early exposure to As was linked to memory deficits and
771 intellectual disabilities (Tolins *et al.*, 2014). Studies in animal models confirmed the link between As
772 exposure, cognitive deficits and alteration of myelinated fibers (Niño *et al.*, 2020). In male rats,
773 environmentally-relevant As exposure during gestation and postnatal development induced chronic
774 hypomyelination, evidenced by a decrease in MBP expression in prefrontal cortex and/or corpus
775 callosum at 2 to 12 months of age (Niño *et al.*, 2020). These changes in white matter, designating the
776 developing myelin sheath as a target of As, might participate in As-associated cognitive deficits
777 observed in human populations and animal models. In this model, As exposure also induced an
778 increase in mitochondrial mass in the brain which could contribute to restore conduction in
779 hypomyelinated axons. However, this increase could also participate in oxidative stress generation,
780 to which OLs are particularly vulnerable (Niño *et al.*, 2020). In this context, an *in vitro* study
781 demonstrated a negative impact of oxidative stress on OLs differentiation from human and rat NPCs
782 (Masjosthusmann *et al.*, 2019). In female rats exposed to As (3 to 36 ppm in drinking water) during
783 gestation, lactation and until 1 to 4 months of age, myelin damage was dose-dependent, and was
784 notably revealed by empty spaces in fiber tracts of As-exposed animals (Ríos *et al.*, 2009; Zarazúa *et al.*
785 *et al.*, 2010). At low-dose exposure, As induced a decrease in striatal nitric oxide (NO) markers such as
786 NO metabolites, without modifying oxidative stress markers (ROS and lipid peroxidation), suggesting
787 that As neurotoxicity involved a nitrenergic deficit (Ríos *et al.*, 2009). Besides, myelin damage was

788 accompanied by decreased arginine methylation (Zarazúa *et al.*, 2010). Indeed, As metabolism
789 requires high amounts of methyl donor S-adenosylmethionine (SAM). Arsenic exposure can thus
790 lead to SAM depletion, and, consequently, to hypomethylation of proteins and other molecules.
791 Because MBP methylation is important for myelin compaction and assembly, these results suggested
792 that As could exert its toxicity towards myelin by causing SAM depletion (Zarazúa *et al.*, 2010). Since
793 estrogens are involved in regulation of methylation, As neurotoxicity could possibly implicate
794 endocrine disrupting mechanisms (Zarazúa *et al.*, 2010).

795 Besides critical windows of development, As is also neurotoxic in adult. Positive correlations were
796 observed between chronic As exposure in adults and decreased cognitive function (Karim *et al.*,
797 2019). Acute exposure can also lead to memory trouble, confusion and anxiety (Rodríguez *et al.*,
798 2003). Anomalies of structure and compaction of myelin in the hippocampus have been reported in
799 male rats chronically exposed to As (Jing *et al.*, 2012). In agreement with these data, chronic
800 exposure of adult male rats to As for 28 days induced myelin sheath loss in the frontal cortex and the
801 hippocampus (Srivastava *et al.*, 2014). In this model, As triggered apoptosis by inhibiting
802 mitochondrial complexes, altering mitochondrial membrane permeability and decreasing membrane
803 potential. These deleterious effects, which were associated with ROS generation, were reversed by
804 concomitant administration of curcumin (Srivastava *et al.*, 2014). In mice exposed to ancient Chinese
805 medicine realgar, As accumulated in the brain (Zhang *et al.*, 2020). Lipidomic analysis revealed a
806 decrease in the ratio of mono and polyunsaturated FAs to saturated FAs in phosphatidylcholines and
807 phosphatidylserines, while there was an increase of phosphatidylethanolamine that could be
808 compensatory. This effect was dose-dependant and could be due to oxidation. Moreover, there was
809 a general increase in lysophospholipids (lysophosphatidylethanolamines and
810 lysophosphatidylcholines) which are required for autophagy, since the autophagosome is formed by
811 a bilayer of phospholipids. Lysophosphatidylcholine increase plays a role in Ca²⁺ increase, oxidative
812 stress and malondialdehyde formation by lipid peroxidation. However, the main effect of As on
813 myelination may be explained by its ability to regulate phospholipid distribution in cell membrane,
814 therefore changing cellular permeability and causing demyelination (Zhang *et al.*, 2020).

815 In the PNS, As toxicity has been clearly shown to target myelin, since acute intoxication in adult
816 induced demyelinating peripheral neuropathies (Chatterjee *et al.*, 2018; Greenberg, 1996). In
817 addition, a strong association was demonstrated between As containing dust exposure and
818 peripheral neuropathy (Gerr *et al.*, 2000). Similarly, male rats exposed to arsenite showed a
819 reduction in myelin thickness in the sural nerves (García-Chávez *et al.*, 2007). This severe
820 demyelination was accompanied by an altered conduction of action potentials. Myelin sheaths had
821 an irregular shape and degenerated after repeated As exposure, likely associated with lipid

822 peroxidation and consequent oxidative damage (García-Chávez *et al.*, 2007). In humans,
823 investigation of miRNAs in As-exposed individuals revealed an increase in senescence associated
824 miRNAs, especially miR-29a and miR-34a, associated respectively with oxidative stress and p53
825 induced senescence (Chatterjee *et al.*, 2018). In As-exposed individuals, overexpression of miR-29a
826 was even more significant in patients who developed peripheral neuropathy, and the same trend
827 was observed for PMP22 expression (Chatterjee *et al.*, 2018). This result was in apparent
828 contradiction with a previous study demonstrating an inverse relationship between miR-29a and
829 PMP22 (Verrier *et al.*, 2009). Further *in vitro* experiments indicated that miR-29a might up-regulate
830 PMP22 expression by activating the canonical Wnt pathway (Chatterjee *et al.*, 2018). Given the
831 growing evidence identifying miRNAs as targets and intermediates of hormonal regulations, one
832 could speculate that impacts of As on miRNAs expression could involve endocrine-related
833 mechanisms (Cameron *et al.*, 2016). More generally, the epigenetic consequences of EDC exposure
834 are increasingly studied and could help understanding the mechanisms by which early exposures can
835 impact health later in life (Bommarito *et al.*, 2017).

836 3.5. Pesticides

837 3.5.1. Chlorpyrifos

838 Chlorpyrifos is a non-persistent organophosphorus insecticide well known for its neurotoxicity,
839 notably through cholinesterase inhibition (Betancourt *et al.*, 2006; Silva, 2020). Chlorpyrifos is
840 metabolized by the liver into chlorpyrifos oxon, which irreversibly inhibits acetylcholinesterase
841 (Connors *et al.*, 2008). Systemic toxicity in adults seems to be based on cholinesterase inhibition, and
842 signs of intoxication appear when more than 70% of total enzyme is inhibited (Connors *et al.*, 2008).
843 In human cohorts, early exposure to chlorpyrifos at low doses has been associated with adverse
844 effects on cognitive development in children (Grandjean and Landrigan, 2014; Venerosi *et al.*, 2012).
845 The developmental neurotoxicity of this pesticide was also confirmed by many studies in animal
846 models, including at doses far below the threshold of acetylcholinesterase inhibition (Connors *et al.*,
847 2008; Silva, 2020; Venerosi *et al.*, 2012). Chlorpyrifos endocrine disrupting potential emerged from
848 studies associating exposure with increased risk of prostate cancer (WHO, 2012). Chlorpyrifos might
849 not interfere directly with androgen, estrogen or thyroid pathways (Juberg *et al.*, 2013). However, its
850 sexually dimorphic impacts on brain development including on hypothalamic neuroendocrine
851 pathways suggest that chlorpyrifos neurotoxicity involves endocrine disrupting mechanisms
852 (Venerosi *et al.*, 2012). The concerns about chlorpyrifos safety at subtoxic concentrations led several
853 countries to move into banning or restricting its use (Silva, 2020; Venerosi *et al.*, 2012). Importantly,

854 developmental neurotoxicity of chlorpyrifos not only involves neurons but also glial cells (Garcia *et*
855 *al.*, 2003).

856 *In vitro* experiments on CG-4 cells demonstrated a direct impact of chlorpyrifos on viability.
857 Apoptosis was induced independently from cholinergic stimulation, through oxidative stress which
858 was evidenced by a dose-dependent superoxide generation but no increase in superoxide dismutase
859 (SOD) activity (Saulsbury *et al.*, 2009). Indeed, OLs are particularly sensitive to oxidative stress-
860 induced apoptosis, since their concentration in iron, which is essential for myelination, is high and
861 their antioxidant mechanisms are relatively limited (Saulsbury *et al.*, 2009). In an attempt to
862 characterize the cell types and brain regions targeted by chlorpyrifos in the developing brain, its
863 effects have been studied when administered to rats (5mg/kg/day) at prenatal (GD17-20), early
864 postnatal (PND1-4) and postnatal (PND11-14) periods (Garcia *et al.*, 2003). Chlorpyrifos neurotoxicity
865 varied with the window of administration and with sex. When administered at PND11-14, which is
866 considered a peak period for myelination, gliogenesis and axogenesis, chlorpyrifos induced an
867 immediate deficit in MBP protein expression across several brain regions in males. This deficit was
868 still visible at PND30 and was accompanied by deficits in NF68 and NF200 neuroproteins, expressed
869 in neuronal cell bodies and developing axons, respectively. In females, gestational exposure to
870 chlorpyrifos transiently upregulated MBP and NF68 expressions, which might involve direct effects
871 on neural cell differentiation as well as indirect effects through acetylcholinesterase inhibition
872 (Garcia *et al.*, 2003). In this study, early postnatal exposure (PND1-4) did not significantly modify
873 MBP expression and other markers in both sexes. However, another laboratory did observe an effect
874 of chlorpyrifos when given during a slightly more expanded period (PND1-6, 1,5 or 3 mg/kg/day),
875 resulting in decreased expression of genes coding for nerve growth factor (NGF), acetylcholine
876 muscarinic receptor M1 and MAG in the forebrain at PND7 (Betancourt *et al.*, 2006). Decrease in
877 *Mag* expression in both sexes suggested an effect on OLs, which might involve cytotoxicity in OPCs
878 leading to reduced number of OLs and/or a blockade in OL maturation. An increase in GFAP
879 expression was also observed in both sexes, revealing astrocyte reactivity that could be induced by
880 ROS production (Betancourt *et al.*, 2006).

881 Humans chronically exposed to chlorpyrifos had increased levels of autoantibodies (IgA, IgM and
882 IgG) towards central and peripheral myelin proteins (Thrasher *et al.*, 2002). These antibodies may be
883 generated because of cell apoptosis. Some of these subjects also had a significant increase in
884 antithyroid or antithyroglobulin autoantibodies. Moreover, chlorpyrifos along with other
885 organophosphorus insecticides, such as dichlorvos, can provoke organophosphorus-induced delayed
886 neuropathy (OPIDN) characterized by neuronal degeneration and demyelination (El Rahman *et al.*,
887 2018; El-Fawal and McCain, 2008). However, evidence of chlorpyrifos toxicity on peripheral myelin is

888 quite limited and is still lacking for central myelin in adults, contrasting with its well-established
889 developmental neurotoxicity.

890 3.5.2. 2,4-Dichlorophenoxyacetic acid (2,4-D)

891 2,4-D is an herbicide used to control the growth of broadleaf weeds (Konjuh *et al.*, 2008). It was
892 initially classified as an EDC because of its suspected role in the development of hormonal cancers in
893 wildlife (WHO, 2012). This pesticide induced hypomyelination in chicks born from treated eggs
894 (Duffard *et al.*, 1987; Mori de Moro *et al.*, 1986). Myelin FA composition was altered with a decrease
895 of long chain FAs and an increase of saturated FAs (Mori de Moro *et al.*, 1986). A decrease in brain
896 UGT8 activity was also demonstrated after preincubation egg exposure (Duffard *et al.*, 1987).
897 Consistent with this data, myelin lipid deficits were observed in rats exposed to 2,4-D through late
898 lactation (PND15-25) at a dose of 100 mg/kg (Duffard *et al.*, 1996). This treatment reduced the levels
899 of monohexosylceramides, phospholipids and free FAs, and increased cholesteryl esters, with a
900 decreased myelin staining, proving a negative impact of 2,4-D during myelination period (Duffard *et al.*
901 *et al.*, 1996). In addition, postnatal exposure of rats (70 mg/kg/day at PND12-25 or 100 mg/kg/day at
902 PND7-25) caused a decrease in major myelin ganglioside GM1 and in myelin deposition (Rosso *et al.*,
903 2000). Exposure of well-nourished and undernourished rats from PND9 till PND21 to 70 mg/kg/day
904 showed that both 2,4-D and undernourishment had independent hypomyelinating effects (Konjuh *et al.*
905 *et al.*, 2008). Moreover, undernourishment increased sensibility to 2,4-D-induced hypomyelination, and
906 myelin proteins (MBP and PLP) expressions were decreased and well correlated with myelin
907 compaction in 2,4-D treated groups. CNP expression was also decreased in treated animals (Konjuh
908 *et al.*, 2008). Since neuronal death of granular cerebellar cells has been reported *in vitro*, the
909 mechanism by which 2,4-D induced hypomyelination could be indirect by reducing the number of
910 axons to myelinate, or direct by preventing OL maturation, or a combination of both actions (Konjuh
911 *et al.*, 2008). However, no consistent epidemiological evidence has associated 2,4-D exposure with
912 myelin deficiency, and more generally with neurotoxicity, although a possible link with increased
913 incidence of Parkinson disease has been evoked (Burns and Swaen, 2012).

914 3.6. Nicotine

915 Nicotine is a psychoactive chemical found in cigarette smoke that acts on acetylcholine nicotinic
916 receptors (Shi *et al.*, 2009). Nicotine is also an endocrine disruptor, owing to its androgenic activity
917 and its capacity to disrupt estrogen-responsive gene transcription (Hewlett *et al.*, 2017; Kanungo *et al.*
918 *et al.*, 2012). Indeed, increased testosterone levels were observed in smoking women. Maternal
919 smoking was notably linked to increased fetal estrogen levels, altered levels of follicle-stimulating
920 hormone receptor, and disruption of cytochrome P450 enzymes involved in androgen biosynthesis

921 (Hewlett *et al.*, 2017). Importantly, *In utero* tobacco smoke exposure was also associated with
922 adverse behavioral outcomes, mainly ADHD but also conduct disorders, drug addiction, depression
923 and autism, some of these impacts being characterized by sexual dimorphism (Cao *et al.*, 2013b;
924 Pauly and Slotkin, 2008). Experimental studies have been carried out to reinforce the possible role of
925 nicotine in these disorders and to highlight its impacts on myelination. Gestational exposure of rats
926 to nicotine (3 mg/kg, GD4-18) caused sex-dependent myelin defects in the prefrontal cortex and the
927 striatum at adolescence (PND35/36) revealed by abnormal expressions of myelin genes, trophic
928 factors and MBP protein (Cao *et al.*, 2013b). While these expressions were increased in males, they
929 were decreased in females. In addition, the number of OLs was increased in the prefrontal cortex in
930 males but not in females. The authors hypothesized that sex hormones could account for the
931 sexually dimorphic impact of nicotine on myelination. By investigating the myelin alterations in
932 juvenile (PND20/21) and adult (PND59/60) animals, they showed that alterations observed in
933 adolescence were specific to this age group and underlined that this period coincided with the onset
934 (or changes in symptomatology) of many psychiatric diseases (Cao *et al.*, 2013a). They also observed
935 long-term alteration of myelin gene expression in adult females but not in males. In zebrafish, myelin
936 gene transcription was also disrupted in offspring after maternal nicotine exposure. Nicotine
937 exposure (5 to 30 μ M) for 1h or 24h each day for 4 months before breeding altered the expression
938 of *Mbp*, *Plp1b* and *Mpz* genes, causing a decrease of expression at 4 days post-fertilization and,
939 conversely, an increased expression at 14 days (Zhao *et al.*, 2014). Altogether, these studies suggest
940 that early exposure to nicotine could contribute to disrupt myelination.

941 In the adult CNS, nicotine exhibited neuroprotective properties in demyelinating conditions. In a
942 mouse model of EAE, nicotine improved the course of EAE in the spinal cord. While EAE induced an
943 increase in nestin+ GFAP+ cells and a decrease in proliferation of ependymal cells, nicotine reversed
944 these impacts and increased the number of MBP+ and CC1+ mature OLs as well as NG2+ OL
945 precursors (Gao *et al.*, 2015). Nicotine might contribute to the switch of ependymal cells to
946 myelinating OLs through reducing inflammation accompanying EAE. Indeed, this effect was
947 accompanied by a decrease in M1 inflammatory microglia (expressing iNOS) and an increase in M2
948 anti-inflammatory microglia (expressing arginase 1). Total microglia also decreased, as shown by
949 IBA1 staining. The reduction of inflammation and demyelination in the spinal cord by nicotine had
950 already been reported (Gao *et al.*, 2015). In an EAE mouse model, administration of nicotine 2 mg/kg
951 exerted an anti-inflammatory effect through the α 7 nicotinic acetylcholine receptor, resulting in
952 decreased CD4+ T-cell number, CD11b+ monocyte infiltration into the CNS, axonal loss, and
953 demyelination (Nizri *et al.*, 2009). T-cell proliferation was reduced by nicotine as well as Th1 (TNF- α
954 and IFN- γ) and Th17 (IL-17, IL-17F, IL-21 and IL-22) cytokines, while a switch to Th2 was observed.

955 Indeed, Th1 pro-inflammatory cytokines play a role in EAE demyelination while Th2 phenotype is
956 associated with remyelination.

957 In the PNS, little data is available on the effects of nicotine on myelin, and rather indicates a
958 deleterious effect. Indeed, nicotine 3 and 6 mg/kg exposure for one month in adult male rats led to
959 abnormal forms of myelin such as folded loops, herniation of myelin and presence of vacuoles of
960 phagocytosis with myelin debris in sciatic nerves. SCs displayed increased apoptosis and axons were
961 atrophied. Nicotine caused oxidative stress through production of free radicals and
962 malondialdehyde, therefore depleting cellular antioxidants (Sayed *et al.*, 2019).

963 3.7. Pharmaceuticals

964 In this section, we chose to present several pharmaceuticals used as endocrine modulators or
965 displaying endocrine disrupting activity besides their main therapeutic use. Several of these
966 compounds were evidenced as potentially deleterious for myelin, especially those displaying anti-
967 androgenic and anti-thyroid effects such as flutamide and 6-propyl-2-thiouracil (PTU), respectively.
968 Conversely, other pharmaceuticals are considered promising therapeutic options in demyelinating
969 conditions, especially tamoxifen through selective ER modulation, but also fluoxetine, through a less
970 well-established mechanism. This is also the case of genistein, the major soybean phytoestrogen,
971 which is discussed in the last section. However, when such compounds reach the body from a
972 contaminated environment, they could also participate in adverse health effects in humans and
973 wildlife, including potential effects on myelin. For example, deleterious effects have been evidenced
974 on early development and reproductive axis in fishes respectively exposed to tamoxifen and
975 fluoxetine (Mennigen *et al.*, 2017; Xia *et al.*, 2016).

976 3.7.1. Flutamide

977 Flutamide is a nonsteroidal anti-androgenic agent used to treat prostate cancer. It can therefore
978 counteract the effects of endogenous AR ligands, i.e. testosterone and its 5 α -reduced derivative 5 α -
979 dihydrotestosterone (DHT). While DHT is non-aromatizable, neural effects of testosterone can also
980 be independent of AR due to its conversion to estradiol by brain aromatase (Hussain *et al.*, 2013;
981 Yang *et al.*, 2018). In the CNS, ARs are essential for brain masculinization. Regarding myelin, male
982 mice have thicker myelin sheaths and longer myelin segments than females (Abi Ghanem *et al.*,
983 2017). These two sex-based differences were completely abolished, especially in the corpus
984 callosum, after administration of flutamide 1 mg/kg for the first 10 postnatal days. Therefore, a
985 female-like phenotype was observed in males (Abi Ghanem *et al.*, 2017). Moreover, ARs and
986 androgens exert neuroprotective effects in the CNS and the PNS (Hussain *et al.*, 2013; Yang *et al.*,

987 2018). In this regard, flutamide 10 μ M blocked remyelinating effect of testosterone in organotypic
988 cultures of cerebellar slices in which demyelination was induced (Hussain *et al.*, 2013). Flutamide
989 administration in a mouse model of EAE also reversed T4 therapy benefits, showing a possible
990 implication of ARs in mediating indirect effects of thyroid hormone (Matejuk *et al.*, 2005). In rats to
991 which a sciatic nerve reversed autologous nerve transplantation was effectuated, DHT increased the
992 rate of axonal regeneration and boosted MPZ expression, leading to a recovery in motor nerve
993 velocity and improved muscle function. These effects of DHT were abolished by a concomitant
994 administration of flutamide (Yang *et al.*, 2018).

995 3.7.2. 6-propyl-2-thiouracil (PTU)

996 Pharmaceutical agents such as 6-propyl-2-thiouracil (PTU), an anti-thyroid compound used to treat
997 hyperthyroidism, can cause developmental hypothyroidism and associated neurotoxicity. Indeed,
998 PTU exposure at 1 mg/kg/day from GD18 to PND21 caused a decrease in several myelin protein
999 coding genes (*Mbp*, *Plp1*, *Mobp*) during postnatal development (P4, P14, P22) in the cerebral cortex
1000 and the hippocampus (Kobayashi *et al.*, 2009). Decreased gene expressions were still observed in the
1001 hippocampus at PND70. In this study, myelin gene dysregulations emerged from a non-targeted
1002 transcriptome screening by microarray, highlighting the importance of TH signaling in myelin
1003 development. Similarly, in another study, PTU exposure at 10 ppm from GD6 till PND21 increased
1004 GFAP+ cells and altered expression of myelin genes, suggesting suppressed myelination. PTU 3 and
1005 10 ppm also altered OL density in the corpus callosum (MBP, OLIG2+) and the cerebral cortex (MBP).
1006 The volume of the corpus callosum was reduced due to OL loss, which seemed irreversible (Shiraki *et*
1007 *al.*, 2014).

1008 3.7.3. Tamoxifen

1009 Tamoxifen is a selective ER modulator (SERM) that acts as an agonist in some tissues such as brain,
1010 and as an antagonist in others such as breast (Chedrawe *et al.*, 2018; Guptarak *et al.*, 2014). It is FDA
1011 approved to treat breast cancer (Guptarak *et al.*, 2014). Due to ER-mediated regulation of OPC
1012 differentiation, tamoxifen appeared as a therapeutic option for the treatment of demyelinating
1013 diseases. In this regard, encouraging results showed that tamoxifen and its main metabolites, 4-
1014 hydroxytamoxifen and endoxifen, enhance OPC differentiation from rat glial progenitors through ER
1015 activation (Barratt *et al.*, 2016). Tamoxifen consistently promoted differentiation of primary rat OPCs
1016 in a ER-dependent manner (Gonzalez *et al.*, 2016). PKC α inhibition by tamoxifen might contribute to
1017 improve OPC differentiation during demyelination (Gonzalez *et al.*, 2016). Indeed, PKC α is activated
1018 by myelin debris when demyelination occurs, thus blocking OPC differentiation. Importantly,
1019 tamoxifen accelerated remyelination *in vivo* after toxin-induced demyelination in the rat CNS

1020 (Gonzalez *et al.*, 2016). Tamoxifen might also promote remyelination by increasing the expression of
1021 OLIG2 transcription factor, which is involved in OPC maturation (Colón *et al.*, 2018). In addition,
1022 antioxidant, anti-apoptotic and anti-inflammatory effects of tamoxifen have been described in the
1023 CNS. Tamoxifen's neuroprotective effect is sexually dimorphic and may implicate mainly ER α
1024 receptors, but also ER β and GPER/GPR30 (Colón *et al.*, 2018). Sexually dimorphic differences might
1025 be due to a higher basal ER α expression and levels of estradiol in females (Colón *et al.*, 2018). In fact,
1026 estradiol is known to be neuroprotective, notably by reducing OL apoptosis through of ER α /ER β
1027 activation (Franco Rodríguez *et al.*, 2013). Nevertheless, ER α , ER β and GPER/GPR30 expressions in
1028 OPCs were shown to be equivalent in rat neonatal female and male.

1029 The immunomodulatory effects of tamoxifen were extensively investigated, including in the context
1030 of demyelinating diseases. Tamoxifen suppressed myelin specific T-cell proliferation in a EAE mouse
1031 model, suggesting that it might be useful in CNS autoimmune diseases (Bebo *et al.*, 2009). In mice,
1032 tamoxifen prevented EAE development by interfering with autoimmune demyelination, and more
1033 precisely by inhibiting Th2 cells (Chedrawe *et al.*, 2018). Tamoxifen and other pharmaceuticals such
1034 as atypical antipsychotics (clozapine, quetiapine) and PPAR γ agonist pioglitazone also reduced the
1035 destruction of OLs, as well as astrocytes and neurons, by enhancing mitochondrial function. Based
1036 on *in vitro* and *in vivo* experiments, these drugs might also promote remyelination in MS (Chedrawe
1037 *et al.*, 2018). Remyelinating effect of tamoxifen was also evidenced after spinal cord injury (SCI).
1038 Locomotor recovery and neuroprotection were observed in adult male cats with SCI after tamoxifen
1039 administration (de la Torre Valdovinos *et al.*, 2016). Tamoxifen increased rates of myelin-associated
1040 proteins such as MBP, MOG, and CNPase in male rats after SCI (Guptarak *et al.*, 2014). Continuous
1041 administration of tamoxifen induced locomotor recovery, neuroprotection, and remyelination up to
1042 6 hours after injury (Colón *et al.*, 2018). In female rats, locomotor recovery could be achieved up to
1043 24 hours after SCI with administration of tamoxifen, which also preserved white matter from further
1044 damage (Colón *et al.*, 2016). It also reduced microglial and astrocytic activation, therefore decreasing
1045 inflammation and glial scar in rats (Guptarak *et al.*, 2014; Tian *et al.*, 2009). Finally, tamoxifen could
1046 also exert neuroprotection through increased release of transforming growth factor β (TGF β) by
1047 astrocytes (Franco Rodríguez *et al.*, 2013).

1048 3.7.1. Fluoxetine

1049 Unlike the previous examples, fluoxetine is not used in clinic for its endocrine modulator properties.
1050 Indeed, fluoxetine is an antidepressant acting as a selective serotonin reuptake inhibitor. In addition,
1051 fluoxetine is an environmental contaminant, especially in aquatic systems and fish tissues, and has
1052 displayed endocrine disrupting effects. For example, waterborne concentrations as low as 0.54 $\mu\text{g/L}$

1053 produced sex-specific endocrine disrupting effects on the reproduction axis in goldfish (Mennigen *et*
1054 *al.*, 2017). It decreased estradiol and mRNA aromatase levels while increasing luteinizing hormone in
1055 females and exerting an estrogen-like effect in males. **Regarding myelin**, fluoxetine effects were
1056 investigated in a transgenic mouse model of Multiple System Atrophy (MSA), a neurological disorder
1057 characterized by alpha-synuclein (α -syn) accumulation in OLs, and to a lesser extent in neurons (Ubhi
1058 *et al.*, 2012). This accumulation was accompanied by astrogliosis, microgliosis as well as neuron and
1059 myelin loss. Fluoxetine at 18 mg/kg for 28 days attenuated astrogliosis in the hippocampus, myelin
1060 loss in the corpus callosum and neuronal loss in the frontal cortex and the hippocampus. Both MSA
1061 neurodegenerative pathology and motor deficits were reduced (Ubhi *et al.*, 2012). In addition,
1062 fluoxetine 10 mg/kg inhibited oligodendroglial death in adult mice after SCI (Lee *et al.*, 2015). OL
1063 death was inhibited by fluoxetine through reduction of p38 mitogen-activated protein kinase
1064 pathway activation in microglia, thus decreasing pro-nerve growth factor production and
1065 subsequent p75 neurotrophin receptor-mediated apoptosis (Lee *et al.*, 2015). Fluoxetine 20 mg/kg
1066 also modulated the immune response in mice EAE models by acting on antigen-presenting cells and
1067 inducing apoptosis of T-cells, resulting in less pro-inflammatory cytokine production, delayed onset
1068 and reduced severity of EAE (Bhat *et al.*, 2017). Finally, fluoxetine 5 mg/kg prevented anxiety
1069 behaviors and memory loss in streptozocin-induced diabetes in mice by inhibiting astrocyte
1070 activation and preventing myelin and OPC loss in the hippocampus (Yuan *et al.*, 2019). **However, the**
1071 **mechanisms by which fluoxetine exerts such protective effects, possibly implicating estrogen**
1072 **signaling, deserve further investigation.**

1073 **3.8. Phytoestrogens: Genistein**

1074 Phytoestrogens are plant-derived compounds found in a wide variety of foods and can be divided
1075 into 3 categories: isoflavones, lignans and coumestans. After ingestion, hydrolysis and digestive
1076 absorption, they are conjugated in the liver and reach the general circulation (Ohgomori and Jinno,
1077 2019). Phytoestrogens can then activate ERs in adult or in perinatal periods due to their structural
1078 similarity with 17β -estradiol (Rosenfeld, 2019). **Most studies linking phytoestrogens to myelin have**
1079 **focused on the soybean isoflavone genistein, and more specifically on its ability to reduce**
1080 **inflammatory response through ERs in the context of demyelinating disorders.**

1081 In a mouse model of EAE, genistein 200 mg/kg reduced Th17 inflammatory response through IFN- β
1082 upregulation. Migration and infiltration of inflammatory cells into the CNS was therefore inhibited
1083 by upregulation of Toll-like receptors (TLR) 3 and 9, which activated suppressor T-cells and TLR3-
1084 mediated IFN- β production leading to reduced vascular cell adhesion molecule 1 and intercellular
1085 cell adhesion molecule 1 expressions (Dias *et al.*, 2018). Genistein also disrupted the differentiation

1086 of Th0 cells into Th1 cells through reduced levels of IL-12, IFN- γ and TNF- α . Moreover, genistein
1087 increased the expression of anti-inflammatory IL-10. These immune modulations lead to less severe
1088 clinical signs in EAE when genistein was used prophylactically (De Paula *et al.*, 2008; Dias *et al.*,
1089 2018). Genistein 10 mg/kg also decreased astrogliosis and neuronal death in the hippocampus of
1090 male rats after amyloid beta1-40 (A β ₁₋₄₀) injection, allowing improved memory (Bagheri *et al.*, 2013).
1091 In a model of MS based on cuprizone (CPZ) -induced demyelination, genistein (30mg/kg) did not
1092 suppress increased pro-inflammatory cytokines associated with demyelination such as IL-1 β
1093 secreted by microglial cells (Ohgomori and Jinno, 2019). However, it decreased demyelination in the
1094 hippocampus by counteracting CPZ induced mitochondrial dysfunction through ER β , therefore
1095 protecting from the loss of mature OLs. Genistein decreased MBP and MOG loss and reduced the
1096 production of myelin debris, which may result in decreased phagocytosis-related molecules
1097 observed in microglia (Ohgomori and Jinno, 2019). Conversely, genistein did not influence astrocyte
1098 reactivity, which is also induced in this model. Genistein may also protect OLs from CPZ-induced
1099 toxicity by activating mTOR signaling pathway, which is important for OL survival and myelination
1100 (Ohgomori and Jinno, 2019).

1101 Genistein impacts in the PNS were investigated in two rat models of peripheral nerve injury, sciatic
1102 nerve crush injury and complete sciatic nerve transection, both with a subsequent administration of
1103 genistein 20 mg/kg (Ozbek *et al.*, 2017). When administered after peripheral nerve injury, genistein
1104 promoted neurological recovery. Indeed, it increased markers of regeneration such as GAP-43 for
1105 axon regeneration and MBP for myelination, and decreased pro-inflammatory cytokines.
1106 Importantly, the treatment had positive impacts on neurological recovery, notably by lowering
1107 neuropathic pain (Ozbek *et al.*, 2017).

1108 To summarize, genistein displayed neuroprotective effects in both central and peripheral myelin
1109 disorders in animal models. Many other benefits for human health are attributed to soybean
1110 phytoestrogens (Patisaul, 2017). However, the global increase of soy consumption raises some
1111 concerns about their endocrine disrupting properties, especially during pregnancy and childhood.
1112 Indeed, phytoestrogens could potentially disrupt the development of hormonal-sensitive organs,
1113 primarily the reproductive system and the brain (Patisaul, 2017).

1114

1115 **4. Concluding remarks**

1116 Myelin, which is essential for proper nervous system functioning, is particularly vulnerable to
1117 environmental stressors such as EDCs. Several EDCs presented here are suspected to contribute to

1118 myelin defects according to yet understudied molecular mechanisms, or to improve recovery in
1119 demyelinating conditions. Among the described mechanisms, interference with hormonal pathways
1120 were highlighted, mainly with thyroid and sex steroid pathways, which play a key role in myelin
1121 development and homeostasis (Hussain *et al.*, 2013; Jung-Testas and Baulieu, 1998; Kipp and Beyer,
1122 2009; Mughal *et al.*, 2018; Schumacher *et al.*, 2012). Oxidative stress was also found to be involved
1123 in the toxicity of several compounds, this nonspecific toxicity mechanism indeed being particularly
1124 deleterious for OLs (Saulsbury *et al.*, 2009). Neuroinflammation, which is notably involved in
1125 demyelinating diseases, was exacerbated by EDCs such as BPA (Brinkmeyer-Langford *et al.*, 2014).
1126 Autoantibodies against myelin proteins might also contribute to myelin damages induced by several
1127 EDCs including BPA, Hg or chlorpyrifos (H.A. el-Fawal *et al.*, 1996; D. Kharrazian and Vojdani, 2017;
1128 Thrasher *et al.*, 2002). Also, central and peripheral myelin were often differentially affected, which
1129 may depend firstly on whether or not the BBB can be crossed by the chemical, but also on CNS and
1130 PNS specificities notably in lesion repair efficiency.

1131 Through the presented examples, several characteristics of EDC impacts were illustrated, including
1132 sexually dimorphic and non-monotonic dose effects. An emerging field which was not addressed in
1133 this review focuses on the so-called “cocktails effects” of EDCs. These effects can be evidenced by
1134 studying chronic exposures of more realistic mixtures of low dose EDCs, for example those detected
1135 in pregnant women (Repouskou *et al.*, 2020; Svingen and Vinggaard, 2016). In the case of myelin
1136 impacts, the research on individual effects of EDCs on myelin is still needed, but one can assume that
1137 EDC mixtures will exert additive or non-additive, and possibly synergistic or opposing, effects.

1138 An important aspect of environmental toxicology is the characterization of quantifiable molecular
1139 markers to finely evaluate the degree and consequences of exposure. In the case of myelin, OL and
1140 SC specific gene and protein expressions are widely used to study the myelination status. Moreover,
1141 metabolites represent a powerful and complementary option, especially lipids which are the main
1142 constituents of myelin. In several studies, differences in lipid composition and/or activity of enzymes
1143 involved in lipid metabolism have been useful to characterize the impacts of EDCs, especially heavy
1144 metals, and could be increasingly explored in the future. Epigenetic modifications are another
1145 category of promising biomarkers which have been characterized in several studies linking EDCs to
1146 myelin, notably circulating microRNAs (Chatterjee *et al.*, 2018; Ling *et al.*, 2020). More generally,
1147 epigenetic modifications represent potential molecular signatures of EDC exposures (Bommarito *et al.*,
1148 2017). Epigenetics are thus of great interest to understand how early environmental exposures
1149 can be responsible for permanent, delayed, and cumulative effects.

1150 Beyond myelin and neurodevelopmental pathologies, environmental EDCs are suspected to
1151 participate in the increased incidence of chronic pathologies in humans, including fertility issues,
1152 cancer, diabetes and obesity (WHO, 2012). More integrated research is needed to apprehend the
1153 impacts of EDCs on health, in particular when exposure occurs during a critical developmental
1154 period.

1155

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1164

1165 **AUTHORS CONTRIBUTIONS**

1166 VN and ALS participated in selecting and interpreting the relevant literature. VN, OL and ALS
1167 contributed to the conception of the article and to the writing of the manuscript. ALS created the
1168 original figures.

1169

1170 **CONFLICT OF INTEREST**

1171 The authors declare that they have no competing interests.

1172

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