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1 Pesticides at brain borders: impact on the blood-brain barrier,  
2 neuroinflammation, and neurological risk trajectories.

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43 **Abstract**

44

45 Pesticides are omnipresent, and they pose significant environmental and  
46 health risks. Translational studies indicate that acute exposure to high pesticide  
47 levels is detrimental, and prolonged interaction with low-level pesticides, as single  
48 and cocktail, could represent a risk factor for multi-organ pathophysiology, including  
49 the brain. Within this research template, we focus on pesticides' impact on the blood-  
50 brain barrier (BBB) and neuroinflammation, physical and immunological borders for  
51 the homeostatic control of the central nervous system (CNS) neuronal networks. We  
52 examine the evidence supporting a link between pre- and postnatal pesticide  
53 exposure, neuroinflammatory responses, and time-depend vulnerability footprints in  
54 the brain. Because of the pathological role of BBB damage and inflammation on  
55 neuronal transmission from early development, varying exposures to pesticides could  
56 represent a danger, perhaps accelerating adverse neurological trajectories during  
57 aging. Refining our understanding of how pesticides influence brain barriers and  
58 borders could enable the implementation of pesticide-specific regulatory measures  
59 directly relevant to environmental neuroethics, the exposome, and one-health  
60 frameworks.

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69 *1) Brain borders: the blood-brain barrier is a port of entry into the CNS.*

70

71 The brain is evolutionarily shielded, physically and biologically, to ensure a  
72 continuous fine-tuning of brain homeostasis and dependable synaptic transmission.  
73 Three borders exist, namely the blood-brain barrier (BBB), the blood-to-cerebral  
74 spinal fluid (B-CSF) barrier **formed by tight junctions between adjacent choroid plexus**  
75 **(CP) epithelial cells, and the meninges where the CSF is filtered from peripheral**  
76 **blood** (Figure 1; see <sup>1-7</sup> for comprehensive reviews). These structures are the  
77 sentinels of brain stability and immunity, surveilling and enabling exact  
78 spatiotemporal synchronizations of neuronal networks that equate to physiological or  
79 normal behaviors, correct memory, executive functions, development, and **aging** <sup>5,8,9</sup>.  
80 In health, these biological structures strictly control the passage of xenobiotics,  
81 exogenous compounds, toxins, and immune cells from the peripheral blood  
82 circulation into the brain parenchyma <sup>1,4,5,7</sup>. Brain barriers, or borders, represent  
83 sensitive sites where the presence and continuous accumulation of environmental  
84 contaminants could have a negative impact and, in turn, promote a harmful sequel to  
85 the brain <sup>3,5,8,10-12</sup>. Here, we focus on the BBB as the primary interface between  
86 peripheral blood and the brain parenchyma. The BBB is a complex network of  
87 capillaries, with each microvessel anatomically and functionally connected to distinct  
88 groups of neurons, hence the terms neuro-glio-vascular unit (NGVU) and metabolic  
89 neurovascular coupling <sup>1,5</sup>. The anatomical reach and the protection afforded by the  
90 BBB are vast; the human brain contains 20-25 m<sup>2</sup> of capillaries, illustrating the  
91 granular exchange to all brain regions and neuronal networks. The BBB is a multi-  
92 cellular structure formed by endothelial cells, astrocytes, and pericytes,

93 communicating with one another, assembled in basement laminae, surrounded by  
94 microglial cells and neurons within tens of micrometers distances (Figure 2). The  
95 BBB endothelium is highly impermeable due to the expression of specific inter-  
96 cellular tight-junctions<sup>1</sup>. ATP (Adenosine triphosphate)-dependent transporter  
97 proteins (and p450 metabolic enzymes<sup>13,14</sup>) expressed at the endothelium are  
98 instrumental in guaranteeing a highly selective exchange of molecules between the  
99 peripheral blood and the brain. Transcytosis and endocytosis (e.g., caveolins) also  
100 regulate BBB permeability<sup>5</sup>.

101

102 BBB damage participates in CNS diseases<sup>2,3,5,8,12</sup> because it intersects with  
103 neuroinflammation and dysregulates the homeostatic control (e.g., via glial buffering)  
104 of ions, ATP, and neurotransmitter levels necessary for the maintenance of resting  
105 potentials and synaptic transmission<sup>2,15</sup>. These events are detailed in two reviews  
106<sup>15,16</sup>. BBB damage and neuroinflammation are ictogenic and can promote seizures<sup>6-</sup>  
107<sup>8,15,17-19</sup>. BBB damage accelerates neurodegeneration<sup>20,21</sup>, is implicated in the  
108 etiology of encephalopathies and psychiatric conditions, and represents a converging  
109 risk factor for pathological aging<sup>20</sup>, neurological and neuroimmunological disorders  
110<sup>22</sup>. The BBB protects the brain from extra-physiological elements or toxins that could  
111 pathologically interfere with the programmed developmental trajectories<sup>7</sup>.  
112 Collectively, this literature illustrates the neurological dangers associated with  
113 increased BBB permeability and neuroinflammatory changes; it underlines the  
114 necessity of investigating the impact of environmental contaminants on brain barriers  
115 to define elements of vulnerability pertinent to brain health. Within this framework, we  
116 review experimental and clinical evidence for specific classes of pesticides currently  
117 under scrutiny as they may pose exposome threats. We performed a Pubmed and

118 Google Scholar search for the period 2010 to 2022, using combinations of two or  
119 more keywords: pesticides, neurotoxicology, zebrafish, rodent models, blood-brain  
120 barrier, neurovascular unit, tight junctions, neuroinflammation, astrocytes, microglial  
121 cells, neurodegeneration, seizures, psychiatric disorders, and brain development.  
122 Including only two databases and a primary focus on a ten years period are potential  
123 research strategy flaws. We provide a general overview of pesticides at the brain  
124 interfaces and summarize data obtained using *in vitro* and *in vivo* models showing  
125 the impact of pesticides at the NGVU. We examine how pesticides constitute risk  
126 factors for adverse neurological trajectories, focusing on pathological conditions  
127 where BBB damage and neuroinflammation are implicated.

128

129 *2) Pesticides: from environmental omnipresence to brain access.*

130

131 With more than 1700 product formulations and increasing amounts applied in  
132 cropland areas <sup>23</sup> (<https://www.fao.org/faostat/en/#data/EP/visualize>), pesticides raise  
133 environmental and health alarms <sup>24-26</sup>. Pesticides are present in matrices, such as  
134 water bodies <sup>23,24,27-29</sup>, ice <sup>30</sup>, rainwater <sup>31</sup>, coastal areas <sup>32</sup>, soil and sediment <sup>29,31,33</sup>.  
135 Pesticide residues are found in wildlife species <sup>34-36,26</sup>. They can be present in spaces  
136 other than agriculture, including schools, playgrounds, households, recreational  
137 water, or urban green areas <sup>25,26</sup>. Occupational exposure is particularly relevant for  
138 agricultural workers or pesticide manufacturers, with potential exposure to high  
139 concentrations <sup>37,38</sup>. Non-occupational exposures can be significant for residents near  
140 crop fields or pesticide facilities <sup>39-43 44,45</sup>.

141

142           These diversified exposure pathways are associated with detecting pesticides,  
143 or their metabolites, in human body fluids such as breast milk <sup>46,47</sup>, urine <sup>48,49</sup>, blood  
144 <sup>50,51</sup>, cerebrospinal fluid <sup>52</sup>, amniotic fluid <sup>53,54</sup>, umbilical cord serum <sup>55</sup>, saliva <sup>56</sup> and  
145 seminal plasma <sup>27,57</sup>. The main entry routes of pesticides to the human body include  
146 i) dermal absorption for occupational exposure, ii) oral exposure through the food  
147 chain, accidental or intentional ingestion, and iii) inhalation <sup>26,58</sup>. These entry routes  
148 converge into the blood circulation, reaching the brain via specific borders (Figure 2)  
149 where two scenarios are possible: i) a lipophilic and low molecular weight (e.g.,  
150 <400Da) molecule penetrates the BBB through the intact endothelium, reaching the  
151 brain parenchyma; ii) a molecule enters the brain after having damaged the BBB  
152 (e.g., increased permeability). In both circumstances, an extra-physiological molecule  
153 enters the brain and could exert neuroglial toxicity. Importantly, at the BBB, a battery  
154 of ATP-dependent drug transporter proteins represents the first line of defense from  
155 exogenous compounds <sup>13,14,59,60</sup>. Efflux transporters pump lipophilic molecules back  
156 into the peripheral blood from the apical endothelial cell, preventing their entry into  
157 the brain. This ATP-binding cassette (ABC) superfamily includes the efflux  
158 transporter P-glycoprotein (Pgp), which expression levels and activity govern the  
159 exclusion of neurotoxicants from the brain <sup>61,62</sup>, together with the multidrug  
160 resistance-associated proteins (MRPs) and the breast cancer resistance protein  
161 (BCRP). A second family is a solute carrier (SLC) bidirectional transporter (export  
162 and import). Members of the SLC family are described in <sup>63,64</sup>. Table 1 provides  
163 archetypical examples of pesticides transported by ABCs or SLCs superfamilies. This  
164 evidence is comprehensively reviewed in <sup>65-67</sup>, along with relevant in vitro and in vivo  
165 models commonly employed for screening experiments.

166

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168

169

170 3) *Pesticides at the neuro-glio-vascular unit: in vitro studies.*

171

172 *In vitro* models are used to examine the impact of pesticides on BBB  
173 permeability and NGVU cells<sup>68,69 70</sup>. Table 2 presents a list of existing evidence for  
174 each cell type while, in the text, we focus on particular examples. The cellular toxicity  
175 of the organophosphate (OPs) malathion and malaoxon was tested using an *in vitro*  
176 BBB model (endothelial cells BMEC or RBE4) and neuroblastoma cells (SH-SY5Y).  
177 Cell viability was reduced with a significant permeability of malathion and malaoxon  
178 across the BBB. Malathion decreased the expression of endothelial cells tight  
179 junctions (occludins, claudin 5, Zonula occludens (ZO) 1, and ZO2). Paraoxon  
180 affected the BBB *in vitro* by reducing cell viability and junctional mRNA and protein  
181 expression<sup>69,71</sup>. Paraoxon negatively impacted occludin and claudin structures in  
182 human-derived endothelial cells<sup>70</sup>.

183

184 With endothelial cells, astrocytes are a key component of BBB stability and a  
185 neuroinflammatory regulator (Table 2). Astrocyte reactivity directly contributes to BBB  
186 damage. They are sensitive to low-dose OPs. Malathion increased intracellular Ca<sup>++</sup>  
187 concentration and induced cytotoxicity via reactive oxidative species (ROS)  
188 production<sup>72-74</sup>. Chlorpyrifos and parathion on human primary astrocytes caused glial  
189 fibrillary acidic protein (GFAP) astrogliosis<sup>75,76</sup>. The pyrethroid cyfluthrin elicited  
190 inflammatory activations in primary human astrocytes<sup>75</sup>. Lambda-cyhalotrin caused



191 cytotoxicity (24 h exposure) by inducing Ca<sup>2+</sup> entry via store-operated Ca<sup>2+</sup>  
192 channels and Ca<sup>2+</sup> release from the endoplasmic reticulum <sup>72</sup>. Cypermethrin on rat  
193 astrocytes led to apoptosis by disrupting the autocrine/paracrine mode of HB-EGF-  
194 EGFR signaling <sup>77</sup>.

195 We next examine microglia, the principal resident immune brain cells reacting  
196 to pesticide exposure and impacting BBB permeability (Table 2). **Low chlorpyrifos**  
197 **levels (0.3-300 μM)** triggered oxidative stress and pro-inflammatory states.  
198 Chlorpyrifos promoted BV-2 microglial activation, proliferation, increased DNA  
199 damage, generation of oxidative markers, and overexpression of pro-inflammatory  
200 markers <sup>78</sup>. An increase in nitric oxide (NO) levels occurred 24 h after dichlorvos  
201 exposure (10 μM), associated with up-regulation of inducible nitric oxide synthase  
202 (iNOS) and pro-inflammatory cytokines like nitric oxide, TNF-α, and IL-1β <sup>79</sup>. At  
203 concentrations of 25 μM or higher, deltamethrin and permethrin significantly  
204 decreased microglial cell viability in a concentration- and time-dependent manner.  
205 Permethrin- and deltamethrin stimulated microglia morphological transformation  
206 (retraction of cell processes and an amoeboid shape) <sup>80</sup>. In the conditioned medium,  
207 cypermethrin increased PKC-δ and iNOS in primary microglia, Tumor Necrosis  
208 Factor-alpha (TNF-α), and interleukin (IL)-1β. Conditioned media from cypermethrin-  
209 treated microglia induced toxicity in primary rat neurons <sup>81</sup>. Exposure to ranging  
210 concentrations (10–100 μM) of bifenthrin for 24 h decreased microglia viability with  
211 maximal effects at 100 μM. No significant cell death occurred at lower concentrations  
212 (0.1, 1, and 5 μM) <sup>82</sup>.

213

214 In addition to NGVU cells, we here discuss the possible influence of pesticides  
215 on circulating leukocytes (Table 2), critical cells interacting with the BBB to promote  
216 neuroinflammatory changes and vascular damage. Lymphocyte exposure to OPs,  
217 glyphosate, methyl parathion, malathion, and chlorpyrifos led to a significant viability  
218 reduction and DNA damage, including DNA single-strand breaks (SSBs) and DNA  
219 double-strand breaks (DSBs) as well as DNA protein cross-links (DPC) formation<sup>83-</sup>  
220<sup>86</sup>. Monocytes or macrophage-like cells (RAW 264.7) exposed to  $\beta$ -Cypermethrin (24  
221 h) showed cytotoxic effects, with decreased cell viability (35% and 79% with 50  $\mu$ M  
222 and 100  $\mu$ M, respectively), phagocytosis, activation of intrinsic apoptotic pathway and  
223 inhibition of the expressions of pro-inflammatory cytokines. ROS production and  
224 oxidative stress were increased following this exposure<sup>86</sup>. Overall, the immune  
225 system could be a target for the toxic effects of pesticides<sup>87</sup>; however, available  
226 experimental and epidemiological data are insufficient to draw firm conclusions on  
227 the immune-toxic risk associated with environmental contaminants. Comprehensive  
228 studies are needed to unveil how pesticides promote cellular-level modifications with  
229 specificity to peripheral and neuro-immune cross-talk.

230

#### 231 *4) Pesticides at the neuro-glio-vascular unit: in vivo studies.*

232

233 Pesticide exposure during prenatal or juvenile stages represents a risk factor  
234 for negative neurodevelopmental trajectories, including a decline in cognition,  
235 hyperactivity, and autism spectrum disorders<sup>88-91</sup>. Consistent with human  
236 epidemiological studies, experimental data have strengthened the adverse  
237 association between pesticides and neurological outcomes, also introducing a

238 pathological impact on the BBB <sup>92-94</sup>. Table 3 and the text below review data obtained  
239 using rodent and aquatic models. We examine the effects of pesticides (pyrethroids,  
240 OPs, organochlorines (OCs), neonicotinoids, and other agents and mixtures) at the  
241 BBB and the intersection with neuroinflammation.

242

243

244

245 *4.1) Evidence from rodent models.*

246

247 Pyrethroids are insecticides produced as synthetic derivatives of the pyrethrin  
248 extracted from *Chrysanthemum cinerariaefolium* <sup>95</sup>. Their insecticidal properties are  
249 based on altering the voltage-gated Na<sup>+</sup> channels in insect neuronal membranes,  
250 disrupting the Na<sup>+</sup> current in the CNS <sup>96</sup>. The effects of pyrethroids extend to the  
251 voltage-gated-calcium and potassium channels, glutamate, and acetylcholine  
252 receptors <sup>97</sup>. Mice exposed to low concentrations of permethrin (0.3 ppm) during  
253 prenatal and postnatal periods showed impairments in the formation of the neural  
254 circuits, indicated by immature neuron marker (doublecortin) and decreased number  
255 of astrocytes <sup>98</sup>. BBB integrity was not affected in rats exposed to permethrin (0.013,  
256 0.13, 1.3 mg/kg/d) for 60 days <sup>68</sup> (topical application). A follow-up study reported  
257 neuronal cell death and neuronal cytoskeletal abnormalities <sup>68</sup>. Another synthetic  
258 pyrethroid, bifenthrin, administered to adult rats for 60 days (0.6 and 2.1 mg/kg/d),  
259 increased the expression of TNF $\alpha$ , IL-1b, IL-6, nuclear factor erythroid-2 (Nrf2),  
260 cyclooxygenase-2 (cox-2), nuclear factor kappa-light-chain-enhancer of activated B  
261 cells (NF-kB), and prostaglandin E2 (PGE2) in the hippocampus, with enhanced  
262 oxidative stress markers (i.e. malondialdehyde (MDA), protein carbonyls (PCO), NO)

263 and reduced antioxidant defense (i.e. catalase (CAT), superoxide dismutase (SOD),  
264 glutathione peroxidase GPx)<sup>82,99</sup>. These inflammatory events can negatively impact  
265 BBB integrity<sup>5</sup>. Similar results were obtained when cypermethrin was orally  
266 administered to adult rats (1 mg/kg/day) or from gestational day (GD) 7 to post-natal  
267 day (PND) 21 (1.5 mg/kg/d)<sup>100,101</sup>. Microglia activation was triggered by cypermethrin  
268 (1.5 mg/kg twice a week) intraperitoneally injected postnatally in rats<sup>97</sup>; cypermethrin  
269 crossed the BBB, leading to oxidative stress<sup>102</sup>. Allethrin, a pyrethroid-based  
270 mosquito repellent, induced BBB permeability in the developing rat (inhalation)<sup>103</sup>.

271

272 OPs irreversibly bind and inhibit acetylcholinesterase (AChE), preventing  
273 acetylcholine breakdown, leading to its accumulation and the hyperstimulation of  
274 cholinergic receptors<sup>104,105</sup>. OPs are the most studied pesticides in experimental  
275 models, with evidence supporting their etiological role in neurodegeneration (Table 3)  
276<sup>100</sup>. OPs permeate the BBB<sup>106</sup>. Acute and chronic OPs exposure in rodents induces  
277 neuroinflammation, activating glial cells and releasing pro-inflammatory cytokines,  
278 prostaglandins, and chemokines<sup>107,108</sup>. Acute exposure to  
279 diisopropylfluorophosphate resulted in neuronal injury, neurodegeneration, and  
280 neuroinflammation, with the activation of microglia and astrocytes, accompanied by  
281 seizures<sup>109,110</sup>. Chlorpyrifos is gaining attention due to its extensive use and non-  
282 target species effects. It triggers neuroinflammation<sup>111</sup>. Mice exposed to chlorpyrifos  
283 (i.p., 5 mg/kg) for ten days showed no morphological changes in pyramidal neuronal  
284 cells<sup>112</sup>. When similar chlorpyrifos concentration was administered orally in rats for  
285 one month, histopathological alterations of pyramidal neurons occurred<sup>113</sup>.  
286 Chlorpyrifos impaired neurogenesis and synaptic integrity (synaptophysin  
287 immunoreactivity). Thus, chlorpyrifos can cross the BBB<sup>112</sup> detected in the CNS of

288 exposed rodents <sup>114</sup>. Chlorpyrifos dermally applied in adult mice increased GFAP  
289 reactivity <sup>115</sup>, affecting oxidative stress and antioxidant defense <sup>102,113,114</sup>. Signs of  
290 neuroinflammation were reported when female mice were exposed to high  
291 concentrations of glyphosate-based herbicides during pregnancy and lactation.  
292 Glyphosate activates microglia and astrocytes and affects synaptic plasticity in the  
293 pup hippocampus <sup>116</sup>; it decreases anti-oxidant enzyme activities in the mouse brain  
294 <sup>117</sup>.

295 OCs, such as DDT, hexachlorocyclohexane (HCH), aldrin, or dieldrin, are  
296 used in certain countries because of their low cost and effectiveness in controlling  
297 insect-borne diseases (e.g., malaria) <sup>118,119</sup>, with long persistence and  
298 bioaccumulation. OCs trigger neurotoxicity, blocking subunits of the GABA-A  
299 receptors. Orally administered endosulfan (28 days, 5 mg/kg/d) to adult rats elicited  
300 oxidative stress and deregulated the levels of neurotransmitters. Endosulfan can  
301 negatively affect the developing brain by altering dopamine <sup>120 121</sup>. Endosulfan  
302 administered to pregnant rats led to cerebellar and hippocampal inflammatory  
303 pathways in the offspring <sup>97,122</sup>. Selective loss of dopaminergic neurons and  
304 disruption of dopamine transport occurred when heptachlor was intraperitoneally  
305 injected in adult mice (7 mg/kg twice a week for 8 weeks) or orally administered to  
306 pregnant mice throughout gestation and lactation (3 mg/kg every 3 days for 2 weeks).  
307 Heptachlor activates astrocytes and microglial cells in specific brain regions, such as  
308 the ventral midbrain area, with dopaminergic system susceptibility to further damage  
309 <sup>123,124</sup>. Methoxychlor injected i.p. for 20 days into adult mice decreased dopamine  
310 levels and disrupted dopamine metabolism and transport, with a link to oxidative  
311 stress at the mitochondrial level. GFAP immunoreactivity was increased <sup>125</sup>.

312

313 Neonicotinoids are nicotinic acetylcholine receptor (nAChR) agonists due to  
314 their structural similarities with nicotine<sup>126</sup>, evoking excitatory responses in the insect  
315 central nervous system. Because of their effects on pollinator populations, some  
316 neonicotinoids (clothianidin, thiamethoxam, imidacloprid) are banned in the EU.  
317 Neonicotinoids were reported to penetrate the BBB poorly, with exceptions in the  
318 brain of mice and zebrafish<sup>127 128</sup>. Neonicotinoids and their metabolites can affect  
319 neurodevelopment and neurotransmission and induce oxidative stress and  
320 neuroinflammation in rodent models<sup>129,130</sup>. Acetamiprid accumulates into the brain  
321 upon a few days of oral ingestion in adult mice, affecting the expression levels of  
322 nAChR without causing gross histomorphological brain changes<sup>131</sup>. Exposure to  
323 acetamiprid and imidacloprid (5 mg/kg day) in postnatal mice reduced neurogenesis  
324 in the hippocampal dentate gyrus and increased the number of activated microglia.  
325 Both neonicotinoids can permeate the BBB<sup>132</sup>; accordingly, imidacloprid and its  
326 metabolites were reported to cross the BBB upon oral exposure to gestational mice  
327<sup>133</sup>, causing oxidative stress and inflammation<sup>134</sup>. Importantly, ROS production exerts  
328 a key role in neonicotinoid-associated neurotoxicity<sup>130 135-137</sup>.

329

330 Paraquat is a well-known neurotoxicant that crosses the BBB<sup>138</sup>, causing  
331 dopaminergic neuronal damage. Paraquat administered to adult mice (i.p, 5 – 80  
332 mg/kg twice a week for 4 weeks) induced neuroinflammation with ROS production in  
333 the substantia nigra, frontal cortex, and hippocampus, with activation of microglia  
334 cells, increased expression of TNF $\alpha$  and IL1 $\beta$ , and dopaminergic neurotoxicity. The  
335 release of pro-inflammatory cytokines from the activated microglia may disrupt the  
336 BBB endothelium<sup>139</sup>. Paraquat (i.p, 1 and 5 mg/kg every 2 days) administered for  
337 several weeks in adult mice augmented BBB permeability. It activated microglia,

338 which release pro-inflammatory cytokines, such as IL-1b, in the dentate gyrus <sup>140</sup>.  
339 When pregnant mice were exposed to paraquat (aerosol), the offspring showed  
340 microglia activation <sup>141</sup>. However, one study did not report neuropathological  
341 alterations in male mice exposed to the maximum tolerated doses of paraquat <sup>142</sup>.

342

343 Rotenone is a natural lipophilic insecticide that interferes with the electron  
344 transport chain. Rotenone can cross the BBB due to its lipophilicity. Two and 3-  
345 weeks of rotenone exposure (i.p) in adult rodents diminished the expression of  
346 endothelial tight junction proteins. Signs of toxicity were reported, such as microglia  
347 and astrocyte activation, neuronal apoptosis, and progressive loss of dopaminergic  
348 neurons. The activation of glial cells was associated with releasing cytokines and  
349 chemokines <sup>143,144</sup>. Atrazine is an herbicide frequently detected in the environment.  
350 Rodents exposed to atrazine via inhalation (25 mg for 28 days) or oral gavage (50 –  
351 200 mg/kg 5 days a week for 45 days) showed neuroinflammation and neurotoxicity,  
352 such as ROS levels and oxidative stress, production of pro-inflammatory cytokines,  
353 microglia activation, and dopaminergic neurons degeneration <sup>145,146</sup>. Other pesticides,  
354 such as ivermectin, a potent insecticide and anthelmintic, were also reported to cross  
355 the BBB <sup>147</sup>.

356

357 Lastly, assessing the effects of a mixture is necessary and a complex task  
358 because the impact of each combination might vary according to the compound and  
359 the doses <sup>148</sup>. We here provide a few examples. Endosulfan and cypermethrin in a  
360 mixture or single components showed dissimilar effects on neuroinflammatory  
361 markers in the hippocampus <sup>97</sup>. Pesticides unable to cross the BBB when used as a  
362 single may quickly enter the CNS when mixed <sup>149</sup>. Permethrin does not alter BBB

363 permeability, but when it was tested with N,N-diethyl-meta-toluamide (DEET), a  
364 decrease of BBB permeability in the cortex occurred<sup>68</sup>. When orally administered to  
365 rats, a mixture of chlorpyrifos and cypermethrin induced oxidative stress<sup>102</sup>. On the  
366 other hand, when chlorpyrifos, methyl parathion, and malathion were administered in  
367 rats, they did not show potentiation of toxicity<sup>150</sup>.

368

369

370

371

#### 372 4.2) Evidence from aquatic models.

373

374 The function of the BBB is conserved across different taxa<sup>151,152</sup>. As in  
375 mammals, fishes have brain endothelial cells, perivascular glia, and pericytes<sup>152</sup>,  
376 affording CNS protection<sup>152</sup>. In harmonization with the rodent data previously  
377 presented, we review the impact of selected compounds (Table 3).

378

379 Pyrethroids can cross the BBB and trigger neurotoxic sequelae in aquatic  
380 animals<sup>95</sup>. Grass carp (*Ctenopharyngodon idella*) exposed to cypermethrin (0.65  
381 µg/L) for 42 days displayed histopathological alterations at the cerebellar level, with  
382 damaged myelin sheath layers and decreased synapses. The genes coding for BBB  
383 tight junction proteins (claudins, occludin, ZO) were downregulated<sup>153</sup>. Common carp  
384 (*Cyprinus carpio*) exposed to deltamethrin (0.04 and 0.08 µM) for 96h showed  
385 degenerative and necrotic neurons at the optic lobe with upregulation of apoptotic  
386 markers as caspase (CAS) 3 and 8. Oxidative stress and inflammatory markers, such  
387 as 8-hydroxy-2'-deoxyguanosine (8-OHdG), iNOS, glutathione S-transferase (GST),



388 and DNA damage were detected in neurons and glial cells of cypermethrin-exposed  
389 carps and rainbow trouts <sup>154-156</sup>; similar results were obtained in neotropical fish  
390 *Prochilodus lineatus* exposed to ng/L levels of  $\lambda$ -cyhalothrin <sup>136,137</sup>. In common carp,  
391 NO vasodilation negatively impacts cerebrovascular structures <sup>152</sup>. Adult and embryo  
392 zebrafish exposed to low concentrations of deltamethrin (0.25 – 2  $\mu$ g/L) showed  
393 persistent alterations in dopaminergic-related gene expression and locomotor activity  
394 <sup>157,158</sup> <sup>159</sup>. Chinook salmon (*Oncorhynchus tshawytscha*) exposed for 96 hours to  
395 environmentally relevant concentrations (0.15 and 1.50  $\mu$ g/L) of bifenthrin presented  
396 neuronal metabolic dysfunction linked to axonal development, as well as apoptotic  
397 and inflammatory activations <sup>160</sup>.

398

399 OPs are studied in aquatic models. Chlorpyrifos is associated with brain  
400 histopathological lesions, neuronal degeneration or death in common carp <sup>161,162</sup>, and  
401 alteration of monoaminergic neurotransmitters in zebrafish embryos <sup>163</sup>. Existing  
402 studies report increased 8-OHdg, CAS3, iNOS immunoreactivity in common carp <sup>161</sup>;  
403 gene transcription for markers associated with neuronal dysfunctions and  
404 neuroinflammatory mechanisms in Atlantic salmon (*Salmo salar*) and common carp  
405 <sup>162,164</sup>; deregulation of the antioxidative system, such as SOD, GST, glutathione  
406 reductase (GS) or catalase (CAT) activities and elevated lipid peroxidation (LPO) and  
407 MDA, a secondary LPO product, in guppy fish brain (*Poecilia reticulata*) and common  
408 carp <sup>162</sup>. Deregulated ROS activities occur with trichlorfon and parathion exposures in  
409 catfish (*Rhamdia quelen*) and common carp <sup>162,165</sup>. After pesticide exposure,  
410 excessive ROS formation negatively impacts cerebrovascular tight junctions <sup>165</sup>.  
411 Zebrafish embryos exposed to a ranging concentration of chlorpyrifos or bifenthrin  
412 (100 – 300  $\mu$ g/L, 15 and 30  $\mu$ M) showed alterations for oxidative stress markers in

413 the brain, along with the upregulation of genes coding for pro-inflammatory cytokines  
414 (e.g., *tnfa*, *il-1β*, *cox2b*). Bifenthrin downregulates pro-angiogenic BBB genes <sup>166-168</sup>.  
415 Nile tilapia (*Oreochromis niloticus*) exposed to bifenthrin presented oxidative stress  
416 and neuroinflammation markers in the brain <sup>168</sup>.

417

418 Next, OCs such as dichlorodiphenyltrichloroethanes (p,p'-DEE, p,p'-DDD, p,p'-  
419 DDT), drins (dieldrin, aldrin, endrin), hexachlorocyclohexanes (HCHs) and  
420 endosulfan can cross the BBB and are detected in brain tissues of wild fish, e.g.,  
421 from Lake Apopka (FL, USA) and a soybean growing area in Argentina <sup>169,170</sup>. In the  
422 hypothalamus of zebrafish and largemouth bass (*Micropterus salmoides*), dieldrin  
423 (0.03 – 1.8 µg/g and 2.29 mg/kg dry weight feed/d) interferes with the mRNA and  
424 protein levels of T-cell receptors, interleukins, oxidative stress, and cell viability <sup>171,172</sup>.  
425 Similar results were obtained in zebrafish embryos exposed to clethodim (10 – 500  
426 µg/L) <sup>173</sup>.

427

428 Neonicotinoids are studied in freshwater species. Imidacloprid (0.001 -10  
429 mg/L) elicited DNA damage and oxidative stress in brain tissue <sup>136,137,174</sup>. Rainbow  
430 trout exposed to environmentally relevant concentrations of clothianidin (3, 15, 30  
431 µg/L) for 21 days displayed signs of cell damage in the brain and histopathological  
432 lesions such as neuron and glial cell damage in the cerebral cortex <sup>175</sup>. Thifluzamide,  
433 an organofluorine compound from the thiazoles group, was tested in aquatic models.  
434 The environmental impact is significant, as fluoro-containing agrochemicals  
435 decompose into inorganic fluorides, negatively influencing wildlife and contaminating  
436 soil or water <sup>176</sup>. Thifluzamide exhibits adverse effects (oxidative damage, cell  
437 apoptosis, and inflammation) on non-target organisms such as zebrafish embryos

438 (0.19 – 2.85 mg/L), with increased serotonin and norepinephrine levels <sup>177,178</sup>. Next,  
439 avermectins are a group of natural substances generated from the fermented  
440 products of *Streptomyces avermitilis*. Specifically, in invertebrates, avermectins **alter**  
441 electrical transmission by enhancing the effects of glutamate at the glutamate-gated  
442 chloride channel. Goldfish (*Carassius auratus*) exposed for 24h to avermectin (0.039  
443 mg/L) showed upregulated mRNA levels of GABA<sub>A</sub> receptors in the brain <sup>179</sup>.  
444 Ivermectin can accumulate in the brain of gilthead sea bream (*Sparus aurata*) and  
445 rainbow trout, with the risk of GABA<sub>A</sub> extra-physiological activation <sup>180,181</sup>.  
446 Furthermore, fipronil, from the group of pyrazoles, has an opposite modality of action  
447 than avermectins. Fipronil blocks the insect GABA-a channels favoring  
448 hyperexcitability. Insect GABA receptors are structurally similar to vertebrates;  
449 zebrafish exposed to fipronil during early development (0.0003 to 5 mg/L) or  
450 adulthood (100 – 2000 ppb) showed signs of oxidative stress and inflammation  
451 (TNF $\alpha$ , NF- $\kappa$ B, and brain-derived neurotrophic factor, BDNF) in the brain <sup>182,183</sup>.  
452 Similar results were obtained in zebrafish embryos exposed for 96 hours to  
453 glufosinate (0.5 – 5 ppm) <sup>184</sup>.

454

455 Another example is rotenone, a rapidly absorbed lipophilic insecticide that  
456 interferes with the mitochondrial electron transport chain <sup>185</sup>. In zebrafish, rotenone  
457 crosses the BBB, inhibits the respiratory chain, induces oxidative stress, and evokes  
458 neuroinflammation <sup>186</sup>. Zebrafish exposed to a low concentration of rotenone for four  
459 weeks displayed an increase in NO and LPO in the brain. SOD and GST antioxidant  
460 activities were depleted in the brain; genes coding for the pro-inflammatory  
461 interleukins were upregulated <sup>187</sup>. Rotenone also impaired the dopamine system in

462 zebrafish <sup>186</sup>. Ziram, another toxic pesticide from the dithiocarbamate family, showed  
463 similar effects <sup>187</sup>.

464

465 Finally, we address the case of pesticide mixtures <sup>188</sup>. When zebrafish  
466 embryos were exposed to 6 pesticides (boscalid, chlorpyrifos, ziram, thiophanate,  
467 thiacloprid, captan) or their mixture during development, the impact was molecule- or  
468 cocktail-specific <sup>189</sup>. In another study, zebrafish embryos were exposed for 96h to a  
469 pesticide mixture, from low to high levels, based on the environmental concentrations  
470 for each compound. The pesticides chosen were: Abamectin (modulation glutamate-  
471 gated chloride channel), carbaryl and chlorpyrifos (AChE inhibition), fipronil (GABA<sub>A</sub>  
472 antagonist), imidacloprid (nicotinic Ach receptor), methoxychlor (Na channel  
473 modulator). Differentially expressed genes were related to neurogenesis and synaptic  
474 plasticity, e.g., forebrain development (*npas4a*), nerve cell growth and differentiation,  
475 synaptic plasticity, and memory (e.g., *egr1*, *vgf*) <sup>190</sup>. Zebrafish exposed to iprodione  
476 (dixarboximide), pyrimethanil (anilinopyrimidine), pyraclostrobin (strobilurin), and  
477 acetamiprid (neonicotinoid), alone or in combination during embryonal development  
478 showed deregulated expressions for genes coding for cell apoptosis (*cas8*, *cas9*,  
479 *p53*, *bax*), oxidative stress (*cat*, *CuSod*, *MnSod*) and cytokines (*il*, *tnfa*). Expression  
480 of *P53* and *tnf* was primarily modified during exposure to pesticide combinations  
481 compared to individual exposures <sup>191</sup>. The avermectin abamectin, the triazole  
482 difenoconazole, the pyrethroid  $\lambda$ -cyhalothrin, and the neonicotinoid imidacloprid  
483 provoked synergistic or antagonist toxicity when their mixtures were tested in  
484 zebrafish and *Prochilodus lineatus* <sup>137,192</sup>. This emerging evidence underscores the  
485 importance of studying complex mixtures of pesticides, cross-comparing to the effect  
486 of single molecules to unravel synergistic neurotoxic effects.

487

488 *5. Pesticide exposure and CNS diseases.*

489

490 We review the experimental and clinical evidence tracing a link between  
491 pesticide exposure and risk for neuropathological trajectories. Continuous or  
492 repeated exposure to low levels of single pesticides or mixture during susceptible  
493 periods (e.g., pregnancy and childhood) is a matter of high clinical significance  
494 <sup>42,193,194</sup>. We focus on brain pathologies where pesticide exposure is a reported risk  
495 factor and for which BBB damage and neuroinflammation play key roles.

496

497

498 *5.1) Neurodegeneration.*

499

500 Exposure to pesticides is a risk factor for adverse neurodegenerative  
501 trajectories (see Table 3), including Parkinson's disease (PD) <sup>195</sup>, Alzheimer's  
502 disease (AD) <sup>196</sup>, and amyotrophic lateral sclerosis (ALS) <sup>197</sup> or multiple sclerosis  
503 (MS) <sup>198</sup>. As an archetype example, the neurotoxic metabolite (MPP) of 1-methyl-  
504 4phenyl-1,2,3,6-tetrahydropyridine (MPTP) was reported to cause PD in humans <sup>199</sup>.  
505 An environmental risk for PD was suggested because MPP and the herbicide  
506 paraquat are chemically analogous <sup>200</sup>. Experimental and epidemiological studies  
507 reinforced the association between paraquat exposure and risk for developing PD <sup>195</sup>,  
508 the latter considered an occupational disease in farmers <sup>201</sup>. Experimentally, neonatal  
509 exposure to the OP chlorpyrifos reduced dopaminergic neurons in rats, significantly  
510 increasing microglia and astrocyte reactivity in the substantia nigra <sup>202</sup>. The OP  
511 cypermethrin induced loss of dopaminergic neurons associated with microglia

512 activation <sup>203,204</sup>. However, it remains unclear whether inflammation is a cause or  
513 consequence of cypermethrin-associated PD. Hydrophobic OCs can bind to a  
514 partially folded  $\alpha$ -synuclein conformation, accelerating the fibril deposit process, a  
515 primary biomarker of PD. Other studies demonstrated that OCs lead to oxidative  
516 stress in dopaminergic cells, and  $\alpha$ -synuclein aggregation, highlighting the  
517 importance of these pesticides in PD pathogenesis. Analyses of a cohort of subjects  
518 affected by PD, and living in rural areas with suspected environment pesticides,  
519 showed high level of dichlorodiphenyldichloroethylene (DDE) as compared to a  
520 control population <sup>205</sup>.

521

522

523 Existing meta-analyses suggest pesticide exposure could represent a risk  
524 factor for AD <sup>196</sup>. Notably, the pathological role of inflammation and BBB permeability  
525 in AD was proposed, including plaque-associated microglia exhibiting a reactive  
526 phenotype and passage of serum components into the brain across the damaged  
527 BBB <sup>206</sup>. Chlorpyrifos exposure caused chronic microglial dysregulations and  
528 accelerated neurodegeneration <sup>207</sup>. Cypermethrin elicits upregulation in both A $\beta$  and  
529 (p)-tau in adolescent rats by stimulating a typical pro-  
530 amyloidogenic processing of amyloid precursor protein (APP) through beta-site APP  
531 cleaving enzyme 1 (BACE) and presenilin-1 (PS) <sup>208</sup>. Cypermethrin exposure  
532 promoted oxidative stress and microglial activation <sup>209</sup>. An increased level of A $\beta$  was  
533 reported in an AD model after exposure to chlorpyrifos <sup>210</sup>.

534

535 Environmental factors, including metals, organic solvents, and pesticides, may  
536 contribute to ALS and MS <sup>211</sup>. The increased occupational risk of ALS and MS in  
537 farmers and gardeners could be linked to exposure to glyphosate-based herbicides  
538 <sup>198</sup>. However, the underlying mechanisms remain unclear, with a possible influence of  
539 epigenetics mechanisms. Pesticides can induce different epigenetic alterations in the  
540 expression levels of miRNAs and the modulation of DNA methylation <sup>212-214</sup>. In this  
541 specific field of research, PD is the most documented <sup>215,216</sup>. For example, 20  
542 miRNAs were significantly altered by pesticide exposure. Among these miRNAs, the  
543 hsa-miR-210-3p is particularly interesting as it has been associated with developing  
544 PD <sup>213</sup>.

545

546

547

548 *5.2) Neurodevelopmental and neuropsychiatric disorders.*

549

550 In the developing brain, the forming BBB is vulnerable to toxins. Quinalphos  
551 (OP), cypermethrin (pyrethroid), and lindane (OC) were tested on developing rats,  
552 concluding that oral exposure at critical periods of development could lead to  
553 neurological dysfunction (Table 3), with effects emerging later in life <sup>217</sup>. Pesticides  
554 passing the placental barrier enables this brain vulnerability during pregnancy (Table  
555 4). Immature rats exposed to pyrethroid-based mosquito repellent display similar  
556 pathological patterns impacting BBB permeability <sup>103</sup>. Although the permeability of the  
557 BBB to pyrethroids is limited, the permeability of the immature BBB allows pyrethroid  
558 in the brain resulting in neurologic effects during early development <sup>218</sup>. In turn,

559 elevated levels of pyrethroids in the immature rat brain favor BBB damage because  
560 of neuroinflammation<sup>219,220</sup>.

561

562 Pre- and postnatal exposure to pesticides are associated with a risk for  
563 depressive behavior, mental retardation, and attention deficit or hyperactivity  
564 disorder. The **Chamacos** study showed a relationship between the urine levels of OP  
565 biomarkers in women and the prevalence of attention deficit hyperactivity disorder in  
566 their children<sup>221 222</sup>. Two studies evaluating chlorpyrifos cord blood levels found that  
567 maternal exposure to this OP was associated with decreased working memory and  
568 full-scale IQ<sup>223,224</sup>. Prenatal exposure to malathion was linked with abnormal reflexes  
569 in children<sup>225</sup>. A pilot study on 40 patients presenting glyphosate or glufosinate  
570 intoxication indicated that S100B might be a biomarker for predicting neurologic  
571 complications<sup>226</sup>; its levels in biological fluids indicate BBB cells damage<sup>227-229</sup>.  
572 Experimentally, subchronic exposure to glyphosate (from GD 5 until PND 60) leads to  
573 glutamate excitotoxicity, oxidative damage, and depressive-like behavior associated  
574 with a decreased serum level of S100B<sup>230</sup>. In rodents, prenatal exposure to  
575 deltamethrin increased anxiety; deltamethrin altered cellular adhesion and  
576 vasculature development in *Chd8V986\*/+* mice with autism spectrum disorder-like  
577 phenotypes; the disease phenotype was exacerbated in the mutant mice following  
578 deltamethrin exposure<sup>231</sup>.

579

### 580 *5.3) Seizures and Epilepsy.*

581

582 The societal impact of epilepsy varies worldwide<sup>232,233,234</sup>. A study examined  
583 the prevalence and risk of developing epilepsy in areas of high vs. low pesticide



584 exposure based on agronomic data <sup>235</sup>. The study population consisted of 4007  
585 subjects diagnosed with epilepsy and 580,077 control subjects adjusted for age, sex,  
586 and geographical area. Epilepsy prevalence was significantly higher in areas  
587 associated with elevated pesticide use <sup>235</sup>. Significantly, seizures and epilepsy are  
588 associated with increased BBB permeability <sup>236</sup>; this could facilitate access to  
589 pesticides in the epileptic brain, perhaps accelerating the pathology (Table 3).  
590 Importantly, OPs, acting as potent irreversible cholinesterase inhibitors, can activate  
591 brain cholinergic receptors due to acetylcholine accumulation, initiating a seizure <sup>237</sup>.  
592 Exposure to Paraoxon leads to status epilepticus associated with neuronal damage  
593 <sup>238-240</sup>. The integrity of the BBB is a safeguard against neurotoxic molecules, such as  
594 pesticides, which critically influence its stability. This notion extends to adult life  
595 stages when exposure to environmental pesticides can impact the integrity of the  
596 BBB, influencing or accelerating neurodegeneration.

597

598

599 *6. In search of pathological mechanisms: the example of glyphosate.*

600

601 The molecular mechanisms by which pesticides promote neuro-glio-vascular  
602 toxicity remain elusive because of the high chemical heterogeneity of these  
603 molecules. If we focus on glyphosate, the most utilized herbicide in agriculture,  
604 several avenues have been explored. Biological effect in humans and other  
605 mammals includes oxidative stress and mitochondrial dysfunction, which could  
606 trigger genetic damage, cytotoxicity, biochemical changes, inflammation or  
607 immunosuppression, endocrine disruption, and gut microbiome changes, resulting in  
608 health damage, including neurologic disorders and behavioral and cognitive changes.

609 These impacts of glyphosate have been recently reviewed in <sup>241,242</sup>. Glyphosate could  
610 indirectly interfere with brain function by impacting the microbiota composition.  
611 Glyphosate performs as an inhibitor of 5-enolpyruvylshikimate-3-phosphate synthase  
612 (EPSP synthase), not only in plants but also in bacteria. An inhibiting effect on EPSP  
613 synthase from intestinal microbiota has been reported, affecting mainly beneficial  
614 bacteria. Glyphosate-induced intestinal dysbiosis impacts the CNS, triggering  
615 emotional, neurological, and neurodegenerative disorders <sup>243</sup>. Glyphosate exposure  
616 has been reported to significantly alter brain monoaminergic neurotransmitters levels  
617 (dopamine, serotonin, norepinephrine), in a brain regional- and dose-dependent  
618 manner, in rat <sup>244</sup> and fish <sup>245</sup>; these effects may contribute to its overall spectrum of  
619 neurotoxicity. Eventually, the described effect of pesticides on the permeability of the  
620 BBB may support a direct consequence of glyphosate and its metabolites on  
621 molecular targets of CNS cells, which are not yet well known. For example, acute  
622 glyphosate exposure of rat hippocampal slices (but also chronic exposure *in vivo*)  
623 reduced glutamate uptake and metabolism within glial cells, which is associated with  
624 increased release of this neurotransmitter in the synaptic cleft. Consequently, the  
625 excess of glutamate increases  $Ca^{2+}$  influx in neurons by activating NMDA receptors  
626 and voltage-dependent  $Ca^{2+}$  channels, leading to oxidative stress and neural cell  
627 death <sup>246</sup>. Importantly, glyphosate and its major metabolite, aminomethylphosphonic  
628 acid (AMPA), have structural similarities to glutamate and glycine. Glutamate is the  
629 major excitatory neurotransmitter in the brain, and glycine is the co-agonist required  
630 with glutamate to activate the NMDA type of glutamate receptors. Hence, glyphosate  
631 may also bind directly to the glycine or glutamate binding pocket of NMDA receptors  
632 and affect learning and memory processes driven by this receptor. The case of  
633 glyphosate can be generalized to other compounds when multiple molecular and

634 cellular actions could underlie the toxic effects on the brain. More targeted studies  
635 are required, mainly because the concentrations of environmental contaminants  
636 tested are somehow excessive compared to the daily exposure levels.

637

### 638 *7. Conclusions: pesticides and brain vulnerability.*

639

640 The proposed evidence illustrates how exposure to environmental  
641 contaminants, particularly pesticides, can represent an ecotoxicological and brain  
642 health risk factor. We here offer a few final remarks: first, the duration of exposure  
643 matters. Accumulating evidence shows how pre-clinical studies should re-center on  
644 **real-life risk simulation (long-term, life-long exposure modalities) to mimic adequately**  
645 **environmental and health-relevant scenarios** <sup>247,248</sup>; this experimental paradigm will  
646 enable the discovery of risk factors pertinent to human pathological adaptations or  
647 susceptibility conditions, especially during aging. This consideration leads to our  
648 second remark: levels of exposure matter. While a bulk of past studies focused on  
649 the effect of high-level exposures, recent research is redirecting toward testing the  
650 impact of low levels, from NOAEL (non-observable adverse effect level) to ADI  
651 (acceptable daily intake) established by regulatory agencies. Because most studied  
652 positions within intoxication paradigms, the significance of experimental data to  
653 global human health needs continuous refinements, with difficult cross-comparisons  
654 between experimental and human studies. Key factors include the route of body  
655 entry, levels (with appropriate dose scaling across species), frequency, duration of  
656 contact, specific toxicity, kinetics, metabolism rate, the system's sensitivity, and the  
657 number and types of pesticides tested simultaneously.

658

659 Again, one archetypical example is glyphosate; exposure in rodents negatively  
660 influences neuronal transmission and behavior, although at levels higher than the  
661 ADI <sup>230,249</sup> . Maternal exposure to high levels of glyphosate promotes autistic-like  
662 behavioral deficiencies in murine male offspring <sup>250</sup>. However, current data indicate  
663 that levels of glyphosate in humans are commonly low, although high-exposure  
664 episodes can occur <sup>251,252</sup>. Epidemiological indication supports a link between  
665 glyphosate exposure and neurodevelopmental disorders <sup>253</sup>. Within this framework,  
666 the permeability and the distribution of pesticides at the placental barrier (Table 4)  
667 represent critical elements that will shape the developmental trajectory of the womb.  
668 However, results remain highly debated <sup>254</sup>. Exposure to glyphosate during prenatal  
669 or newborn periods was associated with a risk for attention deficit and hyperactivity  
670 disorders in children with parents previously exposed to glyphosate <sup>255</sup>. However,  
671 these data were insufficient to support public concern for developmental risks <sup>255</sup>.  
672 Importantly, children living in farmworker communities are particularly exposed to  
673 pesticides, such as pyrethroids, OCs, and OPs. In these environments, children could  
674 be at risk (reviewed in <sup>256</sup>).

675 Lastly, the modalities of experimental investigation matter. From molecular to  
676 cellular and physiological levels, it is fundamental to unravel apparent phenotypes  
677 and explain existing discrepancies between studies, experimentally and clinically.  
678 Low exposure levels require sensitive analytical techniques to capture physiological  
679 adaptations. Spatial tissue transcriptomic and single-cell analyses could deliver the  
680 resolution and depth needed to recognize pathway activations with temporal and  
681 regional precisions. The latter could provide a signature corresponding or not to  
682 behavioral phenotypes. For instance, extra-physiological transcript and cellular-level  
683 (e.g., BBB cells) fingerprints were found in response to exposure to low levels of

684 glyphosate in zebrafish larvae, although in the absence of visible brain malformations  
685 or behavioral defects, supporting the notion of subtle and lingering vulnerability  
686 conditions<sup>257</sup>.

687

688 Environmental exposures' ethical and social implications on brain health and well-  
689 being are significant. An emerging neuroethics framework in environmental sciences  
690 seeks possible threats from the continuous interaction between humans and the  
691 environment<sup>258</sup>. The neuro-exposome, from contact with natural matrices to air  
692 pollution, is a principal risk factor for cognitive impairment in young individuals and  
693 abnormal or even accelerated aging trajectories. The finding summarized in this  
694 review support the importance of environmental neuroethics as a contemporary field  
695 of study to identify vulnerability factors that could shape brain health at the population  
696 level or depending on geographic location.

697

698 In summary, refining our knowledge of how environmental pesticides interact  
699 with brain barriers and borders could disclose disease mechanisms inherent to the  
700 exposome, with time- and age-dependent pathological trajectories and susceptibility  
701 elements representing objective risk factors for neurological diseases.

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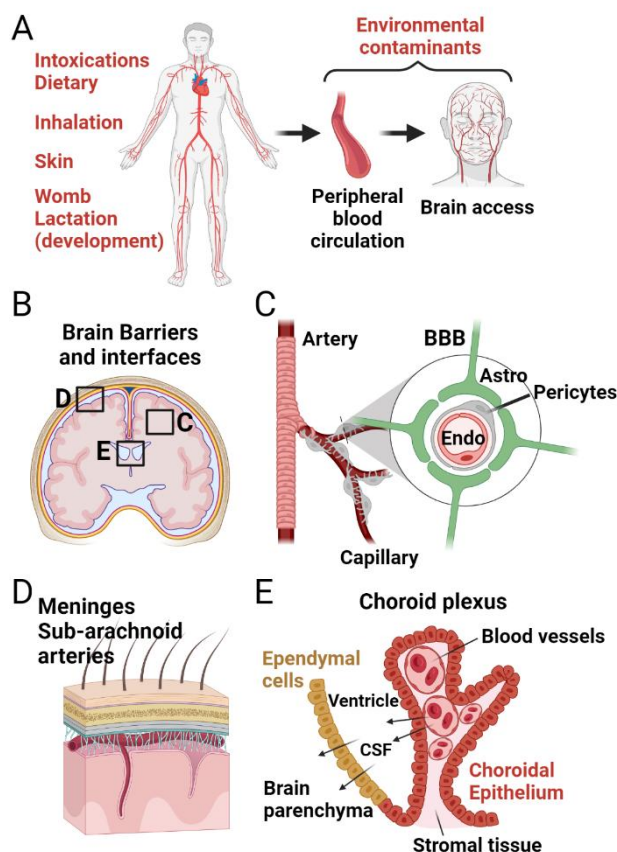
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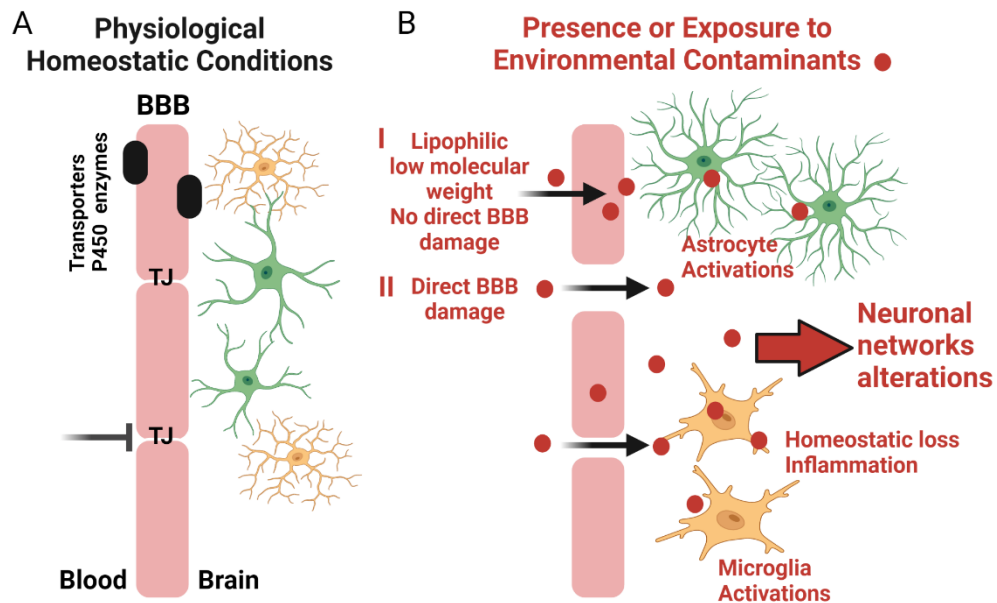
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**Figure 1. Environmental contaminants reach brain borders and barriers. A)** From external matrices, pesticides enter the body, reaching the peripheral blood circulation and the brain. **B-E)** Critical interfaces are the blood-brain barrier (BBB), the meninges with subarachnoid arteries, and the choroid plexus for the production of cerebral spinal fluid (CSF). Specifically, the BBB is a network of capillaries in the brain parenchyma, constituted by a multi-cellular assembly of endothelium, astrocytes, and pericytes. The BBB and adjacent neurons form the neuro-glio-vascular unit.

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**Figure 2. Environmental contaminants, brain-barrier damage, neuroinflammation, and neurological alterations.** A) The BBB is highly impermeable due to tight junctions (TJ), with specific drug transporters regulating the brain entry of specific nutrients. B) From the peripheral blood, I) lipophilic and low molecular weight pesticides could pass through the BBB endothelial cells. Once in the brain, they could affect neuroglia cells enabling inflammation and secondary BBB permeability; II) on the other hand, blood pesticides could directly damage the BBB endothelium (e.g., disrupting TJ), increasing capillary permeability and triggering neuroinflammation. Both scenarios result in pesticide entry into the brain, modifying the parenchymal homeostatic control and altering synaptic transmission in networks.

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**Table 1.** Relevant interactions between pesticides and drug transporters at the BBB.

TRANSPORTE RS	PESTICIDES	REF
ABCs		
Pgp	Diazinon, 1-methyl-4-phenyl-4-phenylpyridinium ion (MPP+), rotenone Methylparathion, endosulfan, cypermethrin, fenvalerate DDT, endosulfan Dibrom, Profenofos	62 259 260
BCRP	DDT, endosulfan Allethrin, tetramethrin, permethrin, resmethrin (pyrethroids) Phosmet, Profenofos	261 260 262
MRP	Allethrin, tetramethrin Profenofos	260 261 262
SLCs		
Amino acid transporters (LATs)	Glyphosate	263
Monocarboxylate transporters (MCTs)	2,4-dichlorophenoxyacetate (2,4-D) Triclopyr	264 265
Organic anion transporters (OATs)	Allethrin, tetramethrin Fenamiphos, malathion, metasystox, profenofos	266 262
Organic anion-transporting polypeptides (OATPs)	Allethrin, tetramethrin Fenamiphos, malathion, parathion, phosmet, profenofos, temephos	64 262
Organic cation transporters (OCTs)	Allethrin, tetramethrin Fenamiphos, fenitrothion, malathion, methyl-parathion, parathion, phosmet, profenofos, propetamphos	64 262
Multidrug and toxin extrusion (MATE)	Allethrin, tetramethrin Fenamiphos, phosmet, propetamphos	64 262

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790 **Table 2.** Environmental pesticides at the BBB and intersections with  
791 neuroinflammation: in vitro studies.

792

PESTICIDE GROUP	COMPOUND	MODEL	DOSE	DURATION	OUTCOMES	PATHWAYS	REF
<b>BBB integrity</b>							
OP	Chlorpyrifos	Neurovascular unit Endothelial cells	NVU: 0, 1, 3, 10, 30, 100 $\mu$ M / Endothelial cells: 0, 10, 30, 100, 300 $\mu$ M	2 h to 24 h	Chlorpyrifos treatment resulted in morphological changes to more circular-shaped cells. The highest exposure tested (300 $\mu$ M) resulted in most cells displaying punctate cell morphology or clumping, indicating cell death. The treatments caused significant disruption of acetylcholine metabolism.	Cell morphology	267
OP	Malathion/oxon	In vitro BBB model (rats' astrocytes, endothelial cells (RBE4 or BMEC), and neuroblastoma cells SH-SY5Y)	1 mM, 100, 10, 1, 0.1, 0.01 $\mu$ M	24 h	Significant decay in cell viability. Malathion and Malaoxon permeability through the barrier (leakage was assessed by measuring the inhibition of AChE enzyme in SH-SY5Y cells in a barrier system)	Cell viability	71
	Malathion Malaoxon	In vitro BBB model (endothelial cells, RBE4 or BMEC)	Malathion $10^{-5}$ M, malaoxon $10^{-6}$ M	2, 4, 8, 16, 24 h	Malathion decreases the proteins associated with tight junction formation	Tight junction proteins occludin, claudin 5, and scaffold ZO1 and ZO2	69
<b>Endothelial cells</b>							
Dipyrids	Paraquat	Human brain microvascular endothelial cells	1, 10, 100 $\mu$ M	24 h	Altered pathways linked to complex I of mitochondrial respiration and significantly decreased mitochondrial function. Modulation of the cholesterol biosynthesis pathway	Mitochondrial function/cholesterol biosynthesis	268

		(HBMECs)					
PYR	Pyrethroid	Microvascular Endothelial Cells	10 $\mu$ M	24 h	No effect on viability; ROS production; Thiobarbituric acid-reactive substances; Protein carbonyl; oxidative stress	Cell viability and ROS production	269
OP	Paraoxon	Human CD34+ derived ECs and bovine brain pericytes	100, 300, 600, 900, 1200 $\mu$ M	24 h	Paraoxon directly affects the BBB in vitro by attenuating viability, integrity, and junctional mRNA and protein expression	Tight junction proteins occludin, claudin 5, and scaffold proteins ZO1 and ZO2 in endothelial cell	70

### Astrocytes / Oligo

OP	Malathion	Gibco® Human Astrocytes (GHA cells), DI TNC1 normal rat astrocytes, BTRG-05MG human glioblastoma cells	20 $\mu$ M to 25 $\mu$ M	20 min	In GHA but not DI TNC1 and DBTRG-05MG cells, malathion induced Ca <sup>2+</sup> release from the endoplasmic reticulum and caused PKC-regulated Ca <sup>2+</sup> influx via 2-APB	Ca <sup>2+</sup> release from the endoplasmic reticulum and Ca <sup>2+</sup> entry via PKC-sensitive store-operated Ca <sup>2+</sup> channels	72
OP	Malathion	Human induced pluripotent stem cell (iPSC)-derived neurons and astrocytes in 3D-matrix	10 <sup>-1</sup> , 10 <sup>-3</sup> , and 10 <sup>-5</sup> M	24 h	A higher astrocyte-to-neuron ratio promotes viability following acute malathion exposure	Cell viability	73
OP	Malathion	Gibco® Human Astrocytes (GHA cells)	0, 5, 10, 15, 20, 25 $\mu$ M	24 h	Cell morphological changes include cell shrinkage, a decrease in cell number, and loss of cell-to-cell contact.	Cell cycle alterations and ROS production	74
OP	Parathion / Chlorpyrifos	Mixed-cell aggregate cultures from fetal rat telencephalon	Parathion: 10 <sup>-9</sup> to 10 <sup>-5</sup> M Chlorpyrifos: 10 <sup>-7</sup> to 10 <sup>-5</sup> M	10 d	Increase in GFAP expression and astrogliosis	Astrocytes reactivity	76
OP	Glyphosate	Rat astrogloma (C6 cells)	40, 80, 160 $\mu$ M	3, 24 h	Decreased cellular viability and mitochondrial respiratory chain activities	Cell viability and mitochondria	270
OP	Chlorpyrifos	Astrocyte-neuron co cultures	10 $\mu$ M to 30 $\mu$ M	48 h	Astrocytes reduce the toxic effect induced by Chlorpyrifos exposure on neurons	Cell viability	271
OP	Diazinon/ Diazoxon	Primary cultures of cortical astrocytes Astrocyte-	0, 0.1, 1, 10 $\mu$ M	24 h	50% decrease in the length of the longest neurite in hippocampal neurons cultured with astrocytes previously treated with 10 $\mu$ M diazinon	Oxidative stress	272

		neuron co-cultures.					
OP/PYR	Chlorpyrifos/cyflutrin	Human primary astrocytes	1, 5, 25 $\mu$ M	7, 14 days.	Upregulation of pro-inflammatory targets	Astrocytes reactivity	75
PYR	Cypermethrin	Astrocytes culture	0–200 $\mu$ M	0, 24, 48 h	Cypermethrin inhibits Epithelial Growth Factor Receptor (EGFR) signaling, reduces EGFR activation-dependent Heparin-Binding-EGF synthesis, attenuates HB-EGF-dependent EGFR expression, promotes apoptosis through the EGFR inactivation in rat astrocytes	Autocrine/paracrine mode of HB-EGF-EGFR signaling at two levels	77
PYR	Lambda-cyhalotrin	Gibco®Human Astrocytes	5-25 $\mu$ M	24 h	Cytotoxicity after 24 h treatment and increased [Ca <sup>2+</sup> ] by inducing Ca <sup>2+</sup> entry via store-operated Ca <sup>2+</sup> channels and Ca <sup>2+</sup> release from the endoplasmic reticulum.	Ca <sup>2+</sup> release	273
<b>Microglia</b>							
PYR	Permethrin and deltamethrin	Immortalized mouse (C57Bl/6) microglial cells, BV2 and primary microglia	0, 0.5, 1, 5, 10, 25, 50, 100 $\mu$ M	24, 48 h	Higher concentrations of permethrin and deltamethrin significantly decrease cell viability and activate microglia cells.	Cell viability and microglia morphology	80
PYR	Cypermethrin	Primary microglia and neuronal culture	0.125 $\mu$ M	48 h	Cypermethrin increases the level of PKC- $\delta$ and iNOS in primary microglia and TNF- $\alpha$ and IL-1 $\beta$ in the conditioned medium. The conditioned media of Cypermethrin-treated microglia induce toxicity in the rat primary neurons.	Pro- and anti-inflammatory cytokines	81
PYR	Bifenthrin	Primary microglia culture and organotypic hippocampal slice (OHSCs)	0,1, 1, 5, 10, 20, 40, 100 $\mu$ M	24 h	Bifenthrin induced a significant decrease in cell viability with higher doses. Bifenthrin does not cause cell death in microglia and astrocytes	Oxidative stress	82
OP	Chlorpyrifos	Immortalized mouse (C57Bl/6) microglial cells, BV2	0.3, 1, 3, 10, 30, 100, 300 $\mu$ M	96 h	Chlorpyrifos triggered oxidative stress and pro-inflammatory states in microglial cells, promoted BV-2 cell activation and proliferation, and increased DNA damage and generation of oxidative markers.	Oxidative stress	79
OP	Dichlorvos	Rat primary microglial cultures	0 to 60 $\mu$ M	24, 36, 48 h	Significant increase in iNOS and NO associated with inflammatory cytokines	Oxidative stress	78
<b>White blood cells</b>							
OP	Malathion	Lymphocytes	1/4 to 1/20 LC <sub>50</sub> (5.2)	2, 4, 8, 12 h	Malathion significantly reduced lymphocyte viability and caused	Cell and DNA viability	84

		suspension (Wistar rats)	mg/L)		DNA damage.		
OP	Glyphosate	Human peripheral whole blood (HMWB)	0.1, 1, 10, 100, 1000, 10000 µM	4, 20 h	Glyphosate alone could not considerably decrease the viability of HMWB cells	Cell viability	85
OP	Methyl parathion/ Chlorpyrifos	Lymphocyte s suspension extracted (Wistar rats)	1/4 to 1/20 LC <sub>50</sub> (0.135 mg/L)	2, 4, 8, 12 h	Malathion significantly reduced rat lymphocyte viability and caused DNA damage.	Cell and DNA viability	84
PYR	β- Cypermethrin	Monocyte/m acrophage- like cells (RAW 264.7 cells)	50 - 100 µM	24 to 48 h	Exposure to β-Cypermethrin reduced cell viability and increased ROS production	Cell viability and ROS production	86

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821 **Table 3.** Environmental pesticides, BBB damage, inflammation, and time-dependent  
822 neuropathophysiology: in vivo studies.

DISEASE	PESTICIDE GROUP	COMPOUND	MODEL AND AGE	DOSE, ROUTE	EXPOSURE DURATION	OUTCOMES	REF
<b>Neurodegenerative diseases</b>							
Alzheimer disease	OP	Chlorpyrifos	Female wild-type (WT) and TgF344-AD rats	10 mg/kg bw/d, subcutaneous injections	Daily for 21 d	Chlorpyrifos induced cognitive impairment associated with the dysregulation of microglia	207
Parkinson's disease	OP	Chlorpyrifos	Sprague-Dawley rats, PND 11 (both sexes)	5 mg/kg bw/d, subcutaneous injection	Daily from PND 11 – 14	Chlorpyrifos induced a significant reduction of dopaminergic neurons and significant activations of microglia and astrocytes in the substantia nigra	202
Parkinson's disease	OP	Cypermethrin	Male Wistar rat pups, PND 5	1.5 mg/kg bw/d, Intra-peritoneal injection	Twice a week from 5-19	Cypermethrin increased the number of macrophages or microglia cells (integrin-Alpha M-positive cells) associated with a reduction of Tyrosine-Hydroxylase-positive cells leading to significant impairment in motor activities	204
Parkinson's disease	OP	Cypermethrin	Male Wistar rat pups, PND 5	1.5 mg/kg bw/d, Intra-peritoneal injection	Twice a week from 5-19, and the rats were re-challenged with 15 mg/kg bw/ twice a week for 12 weeks	Cypermethrin altered motor functions, favored the loss of dopaminergic (TH-positive) neurons, with activated microglial (integrin- $\alpha$ M-positive) cells.	203
Parkinson's disease	Phenylpiazole	Fipronil	Male Sprague Dawley rats, 3 months	15 or 25 $\mu$ g/kg bw/d, microinjections into the substantia nigra	From 7 d to 16 d post-injection	Fipronil exerted a neurotoxic effect on nigrostriatal dopaminergic neurons	274

### Neuropsychiatry Conditions

Depressive disorder	OP	Glyphosate	Adult male Wistar rats	Drinking water, 70 mg/kg bw/d	Maternal exposure from GD 5 to PND 15 or PND 60	Glyphosate induced a depressive-like behavior profile and altered the serum levels of the astrocytic protein S100B.	230
Autism	PYR	Deltamethrin	Chd8V986 <sup>*/+</sup> male mice crossed with C57BL/6J females	3 mg/kg bw/every 3 days mixed into peanut butter	From E0 (maternal exposure to deltamethrin) to PND22	Prenatal exposure to deltamethrin led to increased anxiety along with altered cellular adhesion and vasculature development in Chd8V986 <sup>*/+</sup> mice evaluated at 6 and 12 months of age	231
Attention-deficit/hyperactivity disorder	PYR	Deltamethrin	Adult male and female C57BL/6 mice	0.5 mg/kg bw/d mixed into peanut butter	3 groups: maternal exposure from gestational day (GD) 0 to 5 or GD 6 to 15 and GD 16 to birth	Expression levels of NMDA receptor subunits were decreased in the hippocampus and cerebral cortex of male mice.	275

## Epilepsy

	OP	Paraoxon	Adult male Sprague-Dawley rats	2 mg/kg, one sub-cutaneous administration	Acute treatment, analysis 1h to 1 month and 3 to 6 months	Paraoxon-exposed rats undergo a rapid transition to status epilepticus	240
	OP	Paraoxon	Adult male Sprague-Dawley rats	2 routes: 200 nM to 300 nM intrahippocampal infusions or intra-peritoneal route at 0.35 mg/kg	Acute treatment	Direct injection of 200 nmol paraoxon into the hippocampus caused self-sustaining seizures.	239
	OP	Paraoxon	Adult male Sprague-Dawley rats	450 µg/kg bw/d, one sub-cutaneous administration	Acute treatment, analysis from 2 to 6 weeks after the poisoning	Animals developed generalized tonic-clonic convulsions	276
	OP	Paraoxon	Adult male Sprague-Dawley rats	0.45 mg/kg, intra-muscular injections	Acute treatment, analysis 24 h after poisoning	Paraoxon-treated rats resulted in generalized tonic-clonic convulsions and electrographic evidence of status epilepticus	238

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**Table 4.** Examples of placental transfer in humans, mice, and rats. Detection of pesticides (and their metabolites) in fetal tissues for rodents and placenta/umbilical cord blood for humans.

SPECIE	COMPOUND	TISSUE	REF
MOUSE	Clothianidin (Neonicotinoid)	Fetal tissue	277
	Permethrin, $\alpha$ -cypermethrin (Pyrethroids)	Placenta, fetal body, and amniotic fluid	278
	Azoxystrobin (Strobilurin)	Embryo's brain and placenta	279
RAT	Atrazine, simazine and propazine (Triazines)	Fetal brain and liver	280
	Atrazine (Triazine)	Fetal tissue	281,282
	Permethrin (Pyrethroid)	Fetal liver, brain and blood, and placenta	283
	Fenvalerate (Pyrethroid)	Placenta, fetal liver and testis	284
	Fipronil (Phenyl-pyrazole)	Placenta, amniotic fluid and fetus	285
	Bitertanol (Triazole), propiconazole (Triazole), cypermethrin (Pyrethroid), terbuthylazine (Triazine), malathion (OP)	Amniotic fluid	286
HUMAN	Dichlorodiphenyltrichloroethane (DDTs), hexachlorocyclohexanes (HCHs), and hexachlorobenzene (HCB) (OCs)	Umbilical cord blood and/or placenta	55 287 288 , ,
	DDT and/or HCH (OCs)	Umbilical cord blood and/or placental tissue	289 290 291 292 293 294 295 296 297 , , , , , , , , ,
	DDT, chlordane (CHL), HCH (OCs)	Placental tissue or umbilical cord blood	298 299 ,
	DDT, HCH, aldrin, heptachlor (OCs)	Placental tissue	300
	DDT, HCH, Heptachlor, Endosulfan, Chlordane, Aldrin, Dieldrin, Endrin, Methoxychlor (OCs)	Umbilical cord blood	301
	Aldrin ad Dieldrin (OCs)	Umbilical cord blood	302
	Glyphosate	Umbilical cord blood	303
	2,4-dichloroacetic acid (Phenoxy), prometryn (Triazine), simazine (Triazine), and captan (Phthalimide)	Umbilical cord blood	304
Bendiocarb (Carbamate)	Umbilical cord blood	305	

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